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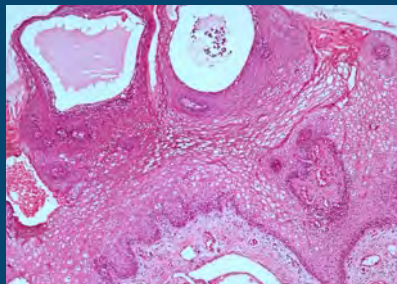
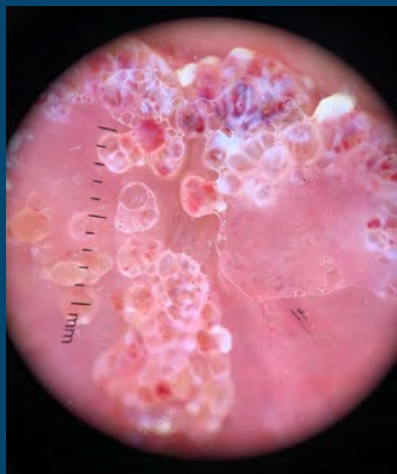
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PARA OS SEUS DOENTES COM PSORÍASE EM PLACAS, MODERADA A GRAVE.¹

IECRM161221
INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

Nome do medicamento Taltz 80 mg solução injetável em caneta/seringa pré-cheia. **Composição qualitativa e quantitativa** Cada caneta/seringa pré-cheia contém 80 mg de ixecizumab em 1 mL. Ixecizumab é produzido em células de Ovírio do Hamster Chinês por tecnologia de ADN recombinante. Lista completa de excipientes, ver “Lista dos excipientes”. **Forma farmacêutica** Solução para injeção (injetável). A solução é límpida e incolor a ligeiramente amarelada. **Indicações terapêuticas** **Psoríase em placas** Taltz é indicado para o tratamento da psoríase em placas, moderada a grave, em adultos que são elegíveis para terapêutica sistémica. **Psoríase em placas pediátrica** Taltz é indicado para o tratamento da psoríase em placas, moderada a grave, em crianças a partir dos 6 anos de idade e com um peso corporal de, pelo menos, 25 kg, e também em adolescentes elegíveis para terapêutica sistémica. **Artrite psoriática** Taltz, em monoterapia ou em associação com o metotrexato é indicado para o tratamento da artrite psoriática ativa em doentes adultos com uma resposta insuficiente ao tratamento com um ou mais fármacos anti-reumáticos modificadores da doença (DMARD) (ver secção 5.1 do RCM). **Espondiloartrite axial** **Espondilite anquilosante (espondiloartrite axial radiográfica)**: Taltz é indicado para o tratamento da espondilite anquilosante ativa em doentes adultos com uma resposta insuficiente à terapêutica convencional. **Espondiloartrite axial não-radiográfica**: Taltz é indicado para o tratamento da espondiloartrite axial não-radiográfica ativa em doentes adultos com sinais objetivos de inflamação, revelados pela elevação da proteína C-reativa (PCR) e/ou imagens de ressonância magnética (RM) e com uma resposta insuficiente a anti-inflamatórios não-esteróides (AINE). **Posologia e modo de administração** Este medicamento deverá ser utilizado sob a orientação e supervisão de um médico com experiência no diagnóstico e tratamento das patologias para as quais é indicado. **Posologia** **Psoríase em placas em adultos**: A dose recomendada é de 160 mg por injeção subcutânea (duas injeções de 80 mg) na semana 0, seguida de 80 mg (uma injeção) nas semanas 2, 4, 6, 8, 10 e 12, e a partir daí uma dose de manutenção de 80 mg (uma injeção) de 4 em 4 semanas (Q4W). **Psoríase em placas pediátrica (a partir dos 6 anos de idade)**: Não estão disponíveis dados de eficácia e segurança em crianças com menos de 6 anos (ver secção 5.1 do RCM). Os dados disponíveis não sustentam a administração em crianças com um peso corporal inferior a 25 kg. A dose recomendada por injeção subcutânea para crianças baseia-se nas seguintes categorias de peso:

Peso corporal da criança	Dose inicial recomendada (semana 0)	Dose recomendada de 4 em 4 semanas (Q4W) daí em diante
Superior a 50 kg	160 mg (duas injeções de 80 mg)	80 mg
25 a 50 kg	80 mg	40 mg

Taltz 80 mg solução injetável em caneta pré-cheia: As doses de ixecizumab de 40 mg devem ser preparadas e administradas por um profissional de saúde qualificado, utilizando a seringa pré-cheia de Taltz 80 mg/1 comercializada. Utilizar a caneta de Taltz 80 mg apenas em crianças que necessitem de uma dose de 80 mg que não precise de ser preparada. Taltz não é recomendado para crianças com um peso corporal inferior a 25 kg. O peso corporal das crianças deve ser registado e revisto periodicamente antes da administração. **Taltz 80 mg solução injetável em seringa pré-cheia**: Para crianças às quais seja prescrita a dose de 80 mg, Taltz pode ser administrado usando diretamente a seringa pré-cheia. Consultar as instruções de preparação de Taltz 40 mg na secção 6.6 do RCM. As doses inferiores a 80 mg devem ser preparadas por um profissional de saúde. Taltz não é recomendado para crianças com um peso corporal inferior a 25 kg. O peso corporal das crianças deve ser registado e revisto periodicamente antes da administração.

Artrite psoriática: A dose recomendada é de 160 mg por injeção subcutânea (duas injeções de 80 mg) na semana 0, seguida de 80 mg (uma injeção) de 4 em 4 semanas. Nos doentes com artrite psoriática e, concomitantemente, com psoríase em placas moderada a grave, a posologia recomendada é a mesma da psoríase em placas. **Espondiloartrite axial (radiográfica e não-radiográfica)**: A dose recomendada é de 160 mg por injeção subcutânea (duas injeções de 80 mg) na semana 0, seguida de 80 mg de 4 em 4 semanas (ver secção 5.1 do RCM para mais informações). Para todas as indicações (psoríase em placas em adultos e crianças, artrite psoriática e espondiloartrite axial) deve ser considerada a interrupção do tratamento em doentes que não tenham demonstrado resposta após 16 a 20 semanas de tratamento. Alguns doentes que inicialmente apresentam apenas uma resposta parcial podem melhorar posteriormente com a manutenção do tratamento para além das 20 semanas. **Populações especiais** **Doentes idosos (> 65 anos)**: Não é necessário ajuste posológico (ver secção 5.2 do RCM). A informação sobre o uso em doentes com idade > 75 anos é limitada. **Compromisso renal ou hepático**: Taltz não foi estudado nestas populações de doentes. Não podem ser feitas recomendações de dose. **População pediátrica** **Psoríase em placas pediátrica (com um peso corporal inferior a 25 kg e com menos de 6 anos de idade)**: Não existe utilização relevante de Taltz em crianças com um peso inferior a 25 kg e com menos de 6 anos para o tratamento da psoríase em placas moderada a grave. **Artrite psoriática pediátrica**: A segurança e a eficácia de Taltz em crianças e adolescentes, entre os 2 e os 18 anos de idade, no tratamento de artrite psoriática (uma categoria da artrite idiopática juvenil) ainda não foram estabelecidas. Não existem dados disponíveis. Não há uso relevante de Taltz em crianças menores de 2 anos para a indicação de artrite psoriática. **Modo de administração** Uso subcutâneo. A administração de Taltz faz-se por injeção subcutânea. Os locais de injeção podem ser alternados. Se possível, as áreas da pele com psoríase devem ser evitadas como locais de injeção. A solução/caneta/seringa não pode ser agitada. Após treino adequado sobre a técnica de injeção subcutânea, a injeção de Taltz pode ser administrada pelo próprio doente, se o médico considerar apropriado. No entanto, o médico deve assegurar um seguimento apropriado dos doentes. As instruções completas para a administração encontram-se no folheto informativo e no manual do utilizador. **Taltz 80 mg solução injetável em seringa pré-cheia**: As doses inferiores a 80 mg que necessitam de preparação só devem ser administradas por um profissional de saúde. Para instruções acerca da preparação do medicamento antes da administração, ver secção 6.6 do RCM. **Contraindicações** Reações de hipersensibilidade grave à substância ativa ou a qualquer um dos excipientes mencionados na “Lista dos excipientes”. Infeções ativas clinicamente relevantes (p. ex. tuberculose ativa, ver “Advertências e precauções especiais de utilização”). **Advertências e precauções especiais de utilização** **Rastreabilidade** De modo a melhorar a rastreabilidade dos medicamentos biológicos, o nome e o número de lote do medicamento administrado devem ser registados de forma clara. **Infeções** O tratamento com Taltz está associado a uma taxa acrescida de infeções, tais como infeções do trato respiratório superior, candidíase oral, conjuntivite e tinea (ver “Efeitos indesejáveis”). Taltz deve ser utilizado com precaução em doentes com infeções crónicas clinicamente relevantes ou com história de infeções recorrentes. Os doentes devem ser instruídos a procurar aconselhamento médico, caso se desenvolvam sinais ou sintomas sugestivos de uma infeção. Caso ocorra uma infeção, os doentes devem ser cuidadosamente monitorizados, e a administração de Taltz deve ser interrompida se o doente não responder ao tratamento convencional ou se a infeção se tornar grave. O doente só deve retomar o tratamento com Taltz após a resolução da infeção. Taltz não pode ser administrado a doentes com tuberculose ativa (TB). Deve ser considerada terapêutica antituberculosa antes do início da administração de Taltz em doentes com tuberculose latente. **Reações de hipersensibilidade** Foram notificadas reações graves de hipersensibilidade, incluindo alguns casos de anafilaxia, angioedema, urticária e, raramente, reações graves de hipersensibilidade retardada (10 a 14 dias após a injeção) incluindo urticária generalizada, dispnéia e altos títulos de anticorpos. Caso se verifique uma reação grave de hipersensibilidade, deve suspender-se imediatamente a administração de Taltz e instituir-se uma terapêutica apropriada. **Doença inflamatória intestinal (incluindo doença de Crohn e colite ulcerosa)** Foram notificados casos de desenvolvimento ou exacerbação de doença inflamatória intestinal com ixecizumab (ver “Efeitos indesejáveis”). O ixecizumab não é recomendado em doentes com doença inflamatória intestinal. Se um doente desenvolver sinais e sintomas de doença inflamatória intestinal ou sentir uma exacerbação de doença inflamatória intestinal pré-existente, o ixecizumab deve ser descontinuado e deve ser iniciado o tratamento médico adequado. **Vacinações** Taltz não deve ser administrado com vacinas de vírus vivos. Não há dados disponíveis sobre a resposta a vacinas vivas; os dados relativos à resposta a vacinas inativas são insuficientes (ver secção 5.1 do RCM). **Excipientes** Este medicamento contém menos de 1 mmol de sódio (3 mg) por cada dose de 80 mg, ou seja, é praticamente “isento de sódio”. **Interações medicamentosas e outras formas de interação** Nos estudos na psoríase em placas, não foi avaliada a segurança de Taltz em associação com outros agentes imunomoduladores ou fototerapia. Em análises farmacocinéticas da população, a eliminação de ixecizumab não foi afetada pela administração concomitante de corticosteróides orais, AINE, sulfasalazina ou metotrexato. **Substratos do citocromo P450** Os resultados de um estudo de interação em doentes com psoríase moderada a grave determinaram que 12 semanas de administração de ixecizumab com substâncias metabolizadas pelo CYP3A4 (i.e. midazolam), CYP2C9 (i.e. varfarina), CYP2C19 (i.e. omeprazol), CYP1A2 (i.e. cafeína) ou CYP2D6 (i.e. dextrometorfano) não tem um impacto clinicamente significativo na farmacocinética dessas substâncias. **Efeitos indesejáveis** **Resumo do perfil de segurança** As reações adversas mais frequentemente notificadas foram reações no local da injeção (15,5%) e infeções do trato respiratório superior (16,4%) (principalmente nasofaringite). **Tabela de reações adversas** As reações adversas observadas nos estudos clínicos e nos relatórios pós-comercialização (Tabela 1) estão listadas por classe de sistemas de órgãos segundo o dicionário MedDRA. Dentro de cada classe de sistemas de órgãos, as reações adversas são ordenadas por frequência, começando pelas mais frequentes. Dentro de cada grupo de frequência, as reações adversas são apresentadas por ordem decrescente de gravidade. Além disso, a categoria correspondente para cada frequência de reações adversas é baseada na seguinte convenção: Muito frequentes (> 1/10); Frequentes (> 1/100 a <1/10); Pouco frequentes (> 1/1.000 a <1/100); Raras (> 1/10.000 a <1/1.000); Muito raras (<1/10.000). No total, foram tratados com Taltz 8.956 doentes em estudos clínicos com e sem ocultação na psoríase em placas, artrite psoriática, espondiloartrite axial e outras doenças autoimunes. Destes doentes, 6.385 foram expostos a Taltz durante pelo menos um ano, o que corresponde cumulativamente a uma exposição em adultos de 19.833 doentes-ano e 196 crianças, o que corresponde cumulativamente a uma exposição de 207 doentes-ano.

Tabela 1. Lista de reações adversas nos estudos clínicos e relatórios pós-comercialização

Classe de sistemas de órgãos	Frequência	Reação adversa
Infeções e infestações	Muito frequentes	Infeção do trato respiratório superior
	Frequentes	Tinha, Herpes simplex (mucocutâneo)
	Pouco frequentes	Gripe, Rinite, Candidíase oral, Conjuntivite, Celulite
Doenças do sangue e do sistema linfático	Pouco frequentes	Neutropenia, Trombocitopenia
Doenças do sistema imunitário	Pouco frequentes	Angioedema
Doenças respiratórias, torácicas e do mediastino	Raras	Anafilaxia
Doenças gastrointestinais	Frequentes	Dor orofaríngea
	Pouco frequentes	Náusea, Doença inflamatória intestinal
Afeções dos tecidos cutâneos e subcutâneos	Pouco frequentes	Urticária, Erupção cutânea, Eczema
Perturbações gerais e alterações no local de administração	Muito frequentes	Reações no local de injeção*

* Ver secção sobre descrição de reações adversas selecionadas. **Descrição de reações adversas selecionadas** **Reações no local da injeção**: As reações no local de injeção observadas com maior frequência foram eritema e dor. Estas reações foram predominantemente de gravidade ligeira a moderada e não obrigaram à descontinuação de Taltz. Nos estudos de psoríase em placas em adultos, as reações no local da injeção foram mais frequentes em indivíduos com um peso corporal < 60 kg em comparação com o grupo com um peso corporal ≥ 60 kg (25 % vs. 14 % para o conjunto dos grupos Q2W e Q4W). Nos estudos da artrite psoriática, as reações no local da injeção foram mais frequentes em indivíduos com um peso corporal < 100 kg em comparação com o grupo com um peso corporal ≥ 100 kg (24 % vs. 13 % para o conjunto dos grupos Q2W e Q4W). Nos estudos de espondiloartrite axial, as reações no local da injeção foram semelhantes em doentes com um peso corporal < 100 kg comparativamente ao grupo com um peso corporal ≥ 100 kg (14 % vs. 9 % para o conjunto dos grupos Q2W e Q4W). O aumento da frequência das reações no local da injeção no conjunto dos grupos Q2W e Q4W não levou a um aumento das descontinuações em nenhum dos estudos de psoríase em placas, artrite psoriática ou espondiloartrite axial. Os resultados descritos acima foram obtidos com a formulação original de Taltz. Num estudo mono-ocultado, cruzado e aleatorizado em 45 indivíduos saudáveis, ao se comparar a formulação original com a formulação revista, sem citrato, foram obtidas pontuações de dor EVA significativamente mais baixas estatisticamente com a formulação sem citrato versus a formulação original, durante a injeção (diferença LSM na pontuação EVA -21,69) e 10 min após a injeção (diferença LSM na pontuação EVA -4,47). **Infeções**: Nos ensaios clínicos de fase III controlados por placebo, na psoríase em placas em adultos, foram notificadas infeções em 27,2% dos doentes tratados com Taltz por um período máximo de 12 semanas em comparação com 22,9% dos doentes tratados com placebo. Na sua maioria, as infeções foram não graves e ligeiras a moderadas, não tendo sido necessário interromper o tratamento na maioria dos casos. Ocorreram infeções graves em 13 (0,6%) dos doentes tratados com Taltz e em 3 (0,4%) dos doentes tratados com placebo (ver “Advertências e precauções especiais de utilização”). Durante todo o período de tratamento, foram notificadas infeções em 52,8% dos doentes tratados com Taltz (46,9 por 100 doentes-ano). Foram reportadas infeções graves em 1,6% dos doentes tratados com Taltz (1,5 por 100 doentes-ano). As taxas de infeção observadas nos estudos clínicos na artrite psoriática e na espondiloartrite axial foram semelhantes às observadas nos estudos na psoríase em placas, com exceção da frequência das reações adversas de gripe e conjuntivite, que foram frequentes em doentes com artrite psoriática. **Avaliação laboratorial de neutropenia e trombocitopenia**: Nos estudos de neutrófilos foi ≥ 1.000 células/mm³. Estes níveis de neutropenia podem persistir, flutuar ou ser transitórios. 0,1% dos doentes tratados com Taltz apresentaram uma contagem de neutrófilos <1.000 células/mm³. Em geral, a neutropenia não obrigou à interrupção de Taltz. 3% dos doentes tratados com Taltz, passaram de uma contagem normal de plaquetas, no início do estudo, para <150.000 plaquetas/mm³ a ≥75.000 plaquetas/mm³. A trombocitopenia pode persistir, flutuar ou ser transitória. A frequência de neutropenia e trombocitopenia nos estudos clínicos na artrite psoriática e na espondiloartrite axial é semelhante à observada na psoríase em placas. **Imunogenicidade**: Aproximadamente 9 a 17% dos doentes adultos com psoríase em placas tratados com Taltz, de acordo com o regime posológico recomendado, desenvolveram anticorpos antifármaco, na sua maioria de baixo título e não associados a uma diminuição da resposta clínica até às 60 semanas de tratamento. No entanto, aproximadamente 1% dos doentes tratados com Taltz apresentaram anticorpos neutralizantes associados a baixas concentrações do fármaco e a uma redução da resposta clínica. Em doentes com artrite psoriática tratados com Taltz de acordo com o regime posológico recomendado até 52 semanas, aproximadamente 11% desenvolveram anticorpos antifármaco, na sua maioria de baixo título, e aproximadamente 8% apresentaram anticorpos neutralizantes. Não se observou qualquer associação aparente entre a presença de anticorpos neutralizantes e o impacto nas concentrações do fármaco ou na sua eficácia. Em doentes com psoríase pediátrica tratados com Taltz de acordo com o regime posológico recomendado até às 12 semanas, 21 doentes (18%) desenvolveram anticorpos antifármaco, aproximadamente metade de baixo título e 5 doentes (4%) apresentaram anticorpos neutralizantes confirmados associados às baixas concentrações do fármaco. Não se observou qualquer associação com a resposta clínica ou com acontecimentos adversos. Em doentes com espondiloartrite axial radiográfica tratados com Taltz com o regime posológico recomendado por um período de até 16 semanas, 5,2% desenvolveram anticorpos antifármaco, na sua maioria de baixo título, e 1,5% (3 doentes) apresentaram anticorpos neutralizantes (NAb). Nestes 3 doentes, as amostras NAB-positivas tinham baixas concentrações de ixecizumab, e nenhum destes doentes atingiu uma resposta ASAS40. Em doentes com espondiloartrite axial não-radiográfica tratados com Taltz com o regime posológico recomendado por um período de até 52 semanas, 8,9% desenvolveram anticorpos antifármaco, todos eles de baixo título; nenhum doente apresentou anticorpos neutralizantes; e não se observou qualquer associação aparente entre a presença de anticorpos antifármaco e a concentração do fármaco, a sua eficácia ou segurança. Para todas as indicações, não ficou claramente estabelecida a existência de uma associação entre imunogenicidade e acontecimentos adversos decorrentes do tratamento. **População pediátrica** O perfil de segurança observado em crianças com psoríase em placas tratados com Taltz de 4 em 4 semanas é consistente com o perfil de segurança em doentes adultos com psoríase em placas, a exceção da frequência de conjuntivite, gripe e urticária, que foram frequentes. A doença inflamatória intestinal também foi mais frequente em doentes pediátricos, embora tenha sido pouco frequente. No estudo clínico pediátrico, verificou-se a ocorrência de doença de Crohn em 0,9% dos doentes do grupo de tratamento com Taltz e 0% dos doentes do grupo placebo durante o período de 12 semanas, controlado com placebo. Verificou-se a ocorrência de doença de Crohn num total de 4 doentes tratados com Taltz (2,0%) durante o período controlado com placebo e de manutenção combinado, no estudo clínico pediátrico. **Notificação de suspeitas de reações adversas** A notificação de suspeitas de reações adversas após a autorização do medicamento é importante. Ela permite uma monitorização contínua da relação benefício/risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do: Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos, Parque da Saúde de Lisboa, Av. Brasil 53. 1749-004 Lisboa. Tel. +351 21 798 73 73. Linha do Medicamento: 800222444 (gratuita). E-mail: farmacovigilancia@infarmed.pt **Data de revisão do texto** 16 de dezembro de 2021. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos: <http://www.ema.europa.eu>. Este medicamento sujeito a recetta médica restrita. Para mais informações devesse



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22º CONGRESSO NACIONAL DE **DERMATOLOGIA E VENEREOLOGIA**

24, 25 e 26 de novembro de 2023
Edifício Egas Moniz - Faculdade de Medicina
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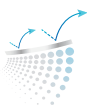
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1 ANO DE IDADE**



**ÚNICO GEL
DE MUPIROCINA
EM PORTUGAL**

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

NOME DO MEDICAMENTO: Impetine® 20mg/g Gel. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA:** Cada grama de gel contém 20 mg de mupirocina (2% p/p de mupirocina). Excipientes: PVP 90 Triglicerídeos de cadeia média (TCM) Alcool isopropílico. **FORMA FARMACÉUTICA:** Gel. Filme de gel transparente e homogêneo. **INDICAÇÕES TERAPÉUTICAS:** Impetine® é indicado para o tratamento das seguintes infeções da pele causadas por organismos suscetíveis: Infeções primárias: impetigo, foliculite e furunculose. Infeções secundárias: dermatite atópica, dermatite eczematosa, dermatite de contato super-infectada e lesões traumáticas infectadas, de uma extensão limitada. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Posologia Adultos (incluindo população idosa, insuficientes hepáticos e renais) e crianças: 1 ano: A posologia recomendada é 2 a 3 vezes por dia durante 5-7 dias, dependendo da resposta. Se depois de 3-5 dias de tratamento com mupirocina não melhorar, o diagnóstico deve ser reconsiderado. Modo de administração: Aplique uma fina camada de gel para cobrir totalmente a área afetada. É importante criar um filme de gel fino e esperar cerca de um minuto até que o produto seque completamente. Não cubra a área tratada com um penso oclusivo ou não oclusivo. As aplicações seguintes do gel devem ser feitas sem retirar ou lavar os restos de produto que permaneçam na área a tratar. Não remova ou limpe os resíduos de gel antes da nova aplicação para evitar a disseminação da infeção. Em caso de lavagem da área, reaplique o produto na área afetada. Crianças: 1 ano: Não existem dados disponíveis de modo a recomendar um regime posológico em crianças. Não misturar com outras preparações, como há um risco de dissolução, e reduzindo a atividade antibacteriana, resultando em perda da estabilidade do gel de mupirocina. **CONTRAINDICAÇÕES:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes. Não existem contraindicações relativas a faixas etárias. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** Caso ocorra uma possível reação de sensibilização ou irritação local grave com a utilização de mupirocina, o tratamento deve ser interrompido, o produto deve ser removido e iniciada terapêutica apropriada. Como outros agentes antibacterianos, o uso prolongado pode resultar no aparecimento de organismos não suscetíveis, incluindo fungos. Impetine® só deve ser administrado por uso cutâneo. Impetine® não é indicado para uso intranasal. Evitar qualquer contacto com os olhos. Se contaminados, os olhos devem ser profusamente irrigados com água. **INTERAÇÕES MEDICAMENTOSAS E OUTRAS FORMAS DE INTERAÇÃO:** Não foram identificadas quaisquer interações medicamentosas com o uso da mupirocina. **EFETOS INDESEJÁVEIS:** Os efeitos indesejáveis são apresentados por ordem decrescente de gravidade dentro de cada classe de frequência. Os efeitos indesejáveis estão classificados por sistemas de órgãos e frequência, são apresentados por ordem decrescente de gravidade dentro de cada classe de frequência. As frequências são definidas como: muito frequentes (≥1/10), frequentes (≥1/100, <1/10); pouco frequentes (≥1/1000, <1/100), raros (≥1/10000, <1/1000), muito raros (<1/10000), desconhecido (não pode ser calculado a partir dos dados disponíveis). Doenças do sistema imunitário. Muito raros: reações alérgicas sistémicas, incluindo anafilaxia, rash generalizado, urticária e angioedema. Afeções dos tecidos cutâneos e subcutâneos: Frequentes: reações de hipersensibilidade no local de aplicação incluindo prurido, eritema, ardor, dermatites de contacto, erupção cutânea. Pouco frequentes: prurido, eritema, ardor e ressecamento da área da aplicação. Reações cutâneas de hipersensibilidade.

Para mais informações deverá contactar o titular da Autorização de Introdução no Mercado:
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edol
saúde que se vê

Informações Essenciais Compatíveis com o Resumo das Características do Medicamento. Bridic 125 mg, comprimidos Um comprimido contém 125 mg de brivudina. Excipientes com efeito conhecido: lactose mono-hidratada. Cada comprimido contém 37 mg de lactose mono-hidratada. **Indicações terapêuticas:** Tratamento precoce do herpes zoster agudo em doentes adultos imunocompetentes. **Posologia e modo de administração:** Adultos: um comprimido de Bridic, uma vez por dia, durante sete dias. O tratamento deve ser iniciado o mais cedo possível, de preferência nas 72 horas seguintes ao aparecimento das primeiras manifestações cutâneas (geralmente o início do rash) ou 48 horas após o aparecimento das vesículas. Os comprimidos devem ser administrados todos os dias, aproximadamente à mesma hora do dia. Se os sintomas persistirem ou se agravarem após os 7 dias de tratamento, o doente deve ser avisado para consultar o médico. O medicamento está indicado em tratamentos de curta duração. Este tratamento reduz adicionalmente o risco de desenvolvimento de nevralgia pós-herpética em doentes acima dos 50 anos de idade, isto é, com a administração da posologia habitual, referida no parágrafo anterior (1 comprimido de Bridic, uma vez por dia, durante 7 dias). Após o primeiro ciclo de tratamento (7 dias), não deve ser iniciado um segundo ciclo. Doentes idosos: Não é necessário ajustamento posológico em doentes com mais de 65 anos de idade. Doentes com insuficiência renal ou hepática: Não se observou alteração significativa na exposição sistêmica da brivudina como consequência da insuficiência renal ou hepática, pelo que não é necessário o ajustamento posológico em doentes com insuficiência renal moderada a grave bem como em doentes com insuficiência hepática moderada a grave. **Contraindicações:** Quimioterapia para cancro com fluoropirimidinas: brivudina é contraindicada em doentes que receberam recentemente ou estão a receber ou estão a planear receber (dentro de 4 semanas) quimioterapia antitumoral com medicamentos contendo 5-fluorouracilo (5-FU), incluindo também as preparações tópicas, os pró-fármacos (como capecitabina, tegafur) e associações de medicamentos contendo estas substâncias ativas ou outras fluoropirimidinas. Terapia antifúngica com flucitossina: brivudina está contraindicada em doentes que receberam recentemente ou estão a receber terapia antifúngica com flucitossina, porque é um pró-fármaco do 5-fluorouracilo (5-FU). A interação entre a brivudina e fluoropirimidinas (por exemplo, capecitabina, 5-FU, etc.) é potencialmente fatal. Doentes imunocomprometidos: brivudina está contraindicada nos doentes imunocomprometidos tais como doentes que receberam recentemente ou estão a receber quimioterapia antitumoral, ou doentes sujeitos a terapia imunossupressora. Crianças: A eficácia e a segurança da brivudina nas crianças não estão estabelecidas, pelo que o seu uso está contraindicado. Hipersensibilidade: a brivudina não deve ser administrada em caso de hipersensibilidade à substância ativa ou a qualquer um dos excipientes Gravidez e lactação: brivudina está contraindicada durante a gravidez ou nas mulheres que estão a amamentar.

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A brivudina não deve ser administrada em doentes que receberam recentemente ou estão a receber ou estão a planear receber (dentro de 4 semanas) quimioterapia antitumoral com medicamentos contendo 5-fluorouracilo (5-FU), incluindo também as suas preparações tópicas, os pró-fármacos (como capecitabina, tegafur) e associações de medicamentos contendo estas substâncias ativas ou outras fluoropirimidinas. A brivudina não deve ser administrada em doentes que receberam recentemente ou estão a receber a terapia antifúngica (com flucitossina) (um pró-fármaco do 5-fluorouracilo). A interação entre a brivudina e fluoropirimidinas (por exemplo, capecitabina, 5-FU, tegafur, flucitossina, etc.) é potencialmente fatal. Casos fatais foram reportados após essa interação medicamentosa. Deve haver um período de espera de pelo menos 4 semanas entre o final do tratamento com brivudina e o início das fluoropirimidinas (por exemplo, capecitabina, 5-FU, tegafur, flucitossina, etc.). No caso de administração accidental de brivudina em doentes que receberam recentemente ou estão a receber fluoropirimidinas, todos os medicamentos devem ser descontinuados e devem ser tomadas medidas eficazes para reduzir a toxicidade dos medicamentos com fluoropirimidina: admissão imediata no hospital e todas as medidas para prevenir a sistêmica infecção e desidratação. Centros especiais de intoxicação (se disponíveis) devem ser contactados o mais rápido possível para encontrar uma ação apropriada contra a toxicidade da fluoropirimidina. A brivudina não deve ser usada se as lesões cutâneas já estiverem completamente desenvolvidas. A brivudina deve ser usada com precaução em doentes com doenças hepáticas crônicas como hepatite. Dados pós-comercialização indicam que estender o tratamento pela duração recomendada de 7 dias aumenta o risco do desenvolvimento de hepatite. Uma vez que a lactose está presente nos excipientes, os doentes com distúrbios hereditários raros de intolerância à galactose, com deficiência de lactase de Lapp ou com síndrome de malabsorção da glicose-galactose não devem tomar este medicamento.

Efeitos indesejáveis: Nos estudos clínicos, a brivudina foi administrada a mais de 3900 doentes. O único potencial efeito adverso mais comum foi a náusea (2,1%). A incidência e o tipo dos potenciais efeitos adversos foram consistentes com os conhecidos com outros agentes nucleosídicos antivirais pertencentes à mesma classe. Os potenciais efeitos adversos da brivudina foram reversíveis e geralmente de intensidade ligeira a moderada. A lista seguinte descreve os potenciais efeitos adversos por órgão - sistema por ordem decrescente de incidência: frequentes (1 - 10%), pouco frequentes (0,1 - 1%), raros (0,01 - 0,1%), desconhecidas. Alterações do sangue e do sistema linfático Pouco frequentes: granulocitopenia, eosinofilia, anemia, linfocitose, monocitose. Raros: trombocitopenia. Doenças do sistema imunitário Pouco frequentes: reações alérgicas / hipersensibilidade (edema periférico e edema de língua, lábio, laringe palébra e na face, prurido, erupção cutânea, aumento da sudorese, tosse, dispneia, broncoespasmo) Alterações do metabolismo e da nutrição Pouco frequentes: anorexia. Perturbações do foro psiquiátrico Pouco frequentes: insónia, ansiedade. Raros Alucinação, estado confusional Desconhecidos: Delírio, inquietação, alterações de humor, humor deprimido. Alterações do sistema nervoso Pouco frequentes: cefaleias, tonturas, vertigens, sonolência. Raras Disgeusia, tremor Desconhecidos Síncopa, distúrbio do equilíbrio, hiperatividade psicomotora Afeções do ouvido e do labirinto Raras Dor de ouvidos Afeções gastrointestinais Frequentes: náuseas. Pouco frequentes: dispepsia, vômitos, dor abdominal, diarreia, flatulência, obstipação. Afeções hepatobiliares Pouco frequentes: fígado gorduroso, aumento das enzimas hepáticas. Raros: hepatite, aumento da bilirrubina no sangue. Desconhecidos Insuficiência hepática grave Afeções cutâneas e dos tecidos subcutâneos Desconhecidos: Erupção fixa, dermatite esfoliativa, eritema multiforme, síndrome de Stevens-Johnson. Afeções musculoesqueléticas e dos tecidos conjuntivos Raras Dores nos ossos. Perturbações gerais e alterações no local de administração Pouco frequentes: astenia, fadiga. Descrição de reações adversas selecionadas: brivudina pode interagir com



Comodidade
posológica

**APENAS
1 POR DIA
X 7 DIAS**



Tratamento precoce do Herpes Zoster agudo em doentes adultos imunocompetentes

- **Potente inibidor da replicação viral (VZ) ¹**
- **Resolução rápida das manifestações cutâneas ¹**
- **Maior prevenção da Nevralgia Pós-Herpética ¹**

(o risco relativo de NPH é 25% menor com Bridic (33% dos doentes) comparado com aciclovir (43% dos doentes) em doentes imunocompetentes com mais de 50 anos tratados para o Herpes Zoster) ¹

agentes quimioterápicos da classe fluoropirimidina. Esta interação que leva a um aumento de toxicidade das fluoropirimidinas, é potencialmente fatal. Os sinais de toxicidade de fluoropirimidinas incluem náusea, vômito, diarreia e, em casos graves estomatite, mucosite, necrose epidérmica tóxica, neutropenia e depressão da medula óssea. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao Infarmed, I.P. (Tel: +351 21 798 73 73; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt; internet: <http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage>). **Titular da Autorização de Introdução no Mercado (A.I.M.): Laboratori Guidotti, S.p.A., Representante Local do Titular da A.I.M.: A. Menarini Portugal - Farmacêutica, S.A., Quinta da Fonte, Edifício D. Manuel I, Piso 2 - A, Rua dos Malhões nº. 1, 2770-071 Paço de Arcos, Portugal, Tel: +351 210 935 500**

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A. MENARINI PORTUGAL FARMACÊUTICA, S.A.
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AJUDA A REDUZIR VISIVELMENTE AS IMPERFEIÇÕES
E MANTÉM A FUNÇÃO DA BARREIRA CUTÂNEA



3 CERAMIDAS ESSENCIAIS



NÃO COMEDOGÉNICO



HIPOALERGÉNICO, FORMULADO PARA
MINIMIZAR O RISCO DE ALERGIA



SEM PERFUME

ATÉ
-21,6%
LESÕES INFLAMATÓRIAS
APÓS 4 SEMANAS¹



ÁCIDO SALICÍLICO



ARGILA HECTORITA



ATÉ
-40%
NO TAMANHO
DAS LESÕES
INFLAMATÓRIAS
EM APENAS 3 DIAS²



ÁCIDO SALICÍLICO



AHAs



TECNOLOGIA MVE

¹ Protocolo: Estudo monocêntrico. 50 mulheres (13-50 anos) com acne leve a moderada e pele normal a oleosa. CeraVe Gel de Limpeza Controlo de imperfeições 2x dia, 4 semanas. Avaliação de eficácia, tolerância e fotografia realizada em T0, T1, T2, T4 e T6 semanas.

² Protocolo: Estudo monocêntrico. 52 mulheres (13-45 anos), com acne leve a moderada e percepção de pele oleosa. Avaliação clínica da eficácia, avaliação da tolerância, avaliação fotográfica e autoavaliação. Uso do Gel Controlo de Imperfeições 1x dia à noite e creme hidratante com fotoproteção de manhã. Avaliação à T2, T4 e T8 semanas.

INOVAÇÃO

ANTHELIOS UVMUNE 400

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A PROTEÇÃO UV MAIS EFICAZ CONTRA OS RAIOS UV MAIS INSIDIOSOS*

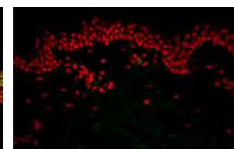
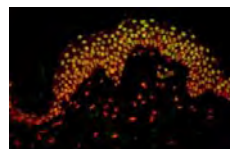
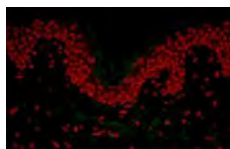


NOVO ESTUDO EX VIVO EM EXPLANTE CUTÂNEO
ALTA EFICÁCIA CONTRA DANOS NO DNA¹

SEM IRRADIAR
(CONTROLO)

IRRADIADO
SEM PROTEÇÃO SOLAR

IRRADIADO
COM PROTEÇÃO SOLAR
UVMUNE 400
OIL CONTROL FLUIDO



FORMAÇÃO DE CPDs
(imunofluorescência verde)

AUSÊNCIA DE FORMAÇÃO
DE CPDs
PROTEÇÃO CONTRA DANO
NO DNA



FÓRMULA MAIS
RESPEITADORA
DA VIDA
MARINHA

*Os mais penetrantes, imperceptíveis a curto prazo, abundantes e durante todo o ano.

¹ Explante cutâneo irradiado por UVB-1,27 J/cm² + UVA-3,8 J/cm². Utilização de câmara de irradiação UV bs-02. Dímeros de pirimidina ciclobutano (CPDs).

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Cover design: Histopathology of the skin biopsy with a dermal granulomatous reaction, predominantly superficial, with periadnexal and perivascular involvement (H&E x40). See article by Freitas et al. in this issue.

Epidemiological analysis of leprosy in Brasil in the past 10 years

Análise epidemiológica da hanseníase no Brasil nos últimos 10 anos

Mariana Dultra^{a*}, Thais Florence^b, Stefanie Gallotti^c, and José R. Pegas^d

Serviço de Dermatologia, Complexo Hospitalar Padre Bento de Guarulhos (CHPBG), São Paulo, Brasil
ORCID: ^a0000-0003-0510-221X; ^b0000-0002-7343-0218; ^c0000-0003-4622-9540; ^d0000-0002-2541-6008

Abstract

Introduction: Leprosy is an infectious and chronic disease caused by *Mycobacterium leprae*. Despite the great worldwide progress after the introduction of multidrug therapy (MDT), leprosy is still considered a major public health problem. The analysis of epidemiological data is important for the implementation of public health policies that allow for breaking the cycle of leprosy transmission and facilitating early diagnosis. **Methods:** This is an observational, cross-sectional, and descriptive epidemiological study. Data were obtained from the Notifiable Diseases Information System (SINAN), the official information system for leprosy in the country. **Results:** During this period, 338,904 cases of leprosy were reported. The northeast region, the one with the most cases, is considered the poorest in the country, with many inhabitants in an unfavorable socioeconomic situation. The majority of multibacillary (MB) patients were associated with late diagnosis, and therefore it maintains the transmission and worsens neurological damage. **Discussion:** The probability of occurrence and reactivation of leprosy was higher in patients with a low level of education, as this class has a low level of knowledge. **Conclusion:** Leprosy has a long incubation period, which increases in adult and elderly cases. Despite the improvements in leprosy control, the disease persists as a public health problem.

Keywords: Leprosy. *Mycobacterium leprae*. Epidemiology.

Resumo

Introdução: A hanseníase é uma doença infecciosa e crônica causada pelo *Mycobacterium leprae*. Apesar do grande avanço mundial após a introdução da poliquimioterapia, a hanseníase ainda é considerada um grande problema de saúde pública. A análise de dados epidemiológicos torna-se importante para a implementação de políticas públicas de saúde que permitam interromper o ciclo de transmissão da doença e facilitar o diagnóstico precoce. **Métodos:** Trata-se de um estudo epidemiológico observacional, transversal e descritivo. Os dados foram obtidos no Sistema de Informação de Agravos de Notificação (SINAN), o sistema oficial de informação sobre hanseníase no país. **Resultados:** Nesse período, foram notificados 338.904 casos de hanseníase. A região nordeste, a que apresenta mais casos, é considerada a mais pobre do país, com muitos habitantes em situação socioeconômica desfavorável. A maioria dos pacientes eram multibacilares, condição associada ao diagnóstico tardio, mantendo a transmissão e agravando o dano neurológico. **Discussão:** A probabilidade de ocorrência e reativação da hanseníase em pacientes com baixa escolaridade foi maior. Além disso, devido ao longo período de incubação, há um maior número de casos em adultos e idosos. Apesar das melhorias no controle da hanseníase, a doença persiste como um problema de saúde pública.

Palavras-chave: Hanseníase. *Mycobacterium leprae*. Epidemiologia.

*Correspondence:

Mariana Dultra
E-mail: dultramariana@hotmail.com

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Introduction

Leprosy is a chronic infectious disease caused by the bacillus *Mycobacterium leprae*, a microorganism that has a tropism for Schwann cells of the peripheral nerves and macrophages of the skin. It has high infectivity and low pathogenicity¹. Although the exact mode of transmission has not been elucidated, close contact with an infected individual in the same household or community is commonly recognized as a high-risk factor for infection^{2,3}. Classically, a case of leprosy is diagnosed when one or more of the following findings are present: skin lesion with altered sensitivity, nerve trunk thickening, or positive skin smear⁴.

The operational classification created by the World Health Organization (WHO) is widely used in programs to combat leprosy around the world. This classification is based on the number of skin lesions: individuals with one to five skin lesions are classified as paucibacillary (PB), while those with six or more are classified as MB⁵.

Multidrug therapy (MDT) is a combination of drugs that is very safe and effective in treating leprosy and preventing the emergence of drug resistance⁵. Currently, the WHO guidelines recommend a three-drug regimen of rifampicin, dapsone, and clofazimine for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and 12 months for MB leprosy⁶. Around the world, MDT is available free of charge to patients who need it upon recommendation of the prescribing physician⁵.

Delayed diagnosis and treatment can lead to nerve damage, loss of muscle function, paralysis, or even permanent disability⁷. It leads to social, economic, and psychological impacts^{1,2}. Therefore, leprosy is still considered a major public health problem in developing countries such as Brazil, India, Myanmar, and Madagascar, even with the great worldwide progress after the introduction of MDT in the 1980s^{1,2}.

The analysis of epidemiological data is important for the implementation of public health policies that allow for breaking the cycle of leprosy transmission, facilitating early diagnosis, and avoiding disabilities.

Objectives

To analyze leprosy indicators in Brazil between 2012 and 2021, considering the number of diagnoses, age range, namely gender, clinical form of the disease, degree of physical impairment, and therapeutic methods.

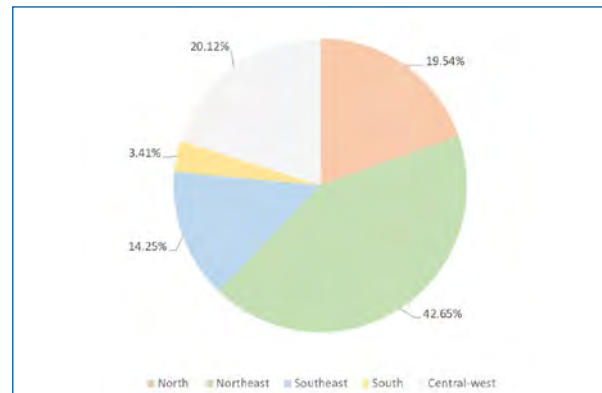


Figure 1. Leprosy cases in each Brazilian region between 2012 and 2021.

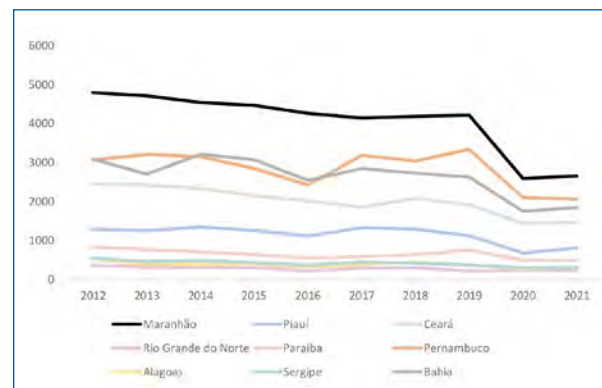


Figure 2. Leprosy cases in the Northeast region between 2012 and 2021.

Materials and methods

This is an observational, cross-sectional, and descriptive epidemiological study. The data were obtained from SINAN, the official information system for leprosy in Brazil, available at the Information Technology Department of the Unified Health System.

Leprosy is part of the National List of Compulsory Notification of Diseases and Public Health Events. Therefore, it is mandatory for health professionals to report cases of the disease on SINAN. These data are collected by professionals from health units by filling in the notification/investigation form and the follow-up bulletin⁴.

This study was conducted exclusively with publicly available secondary data without the identification of subjects that followed ethical principles of resolution 196/96 of the National Health Council, which justified the lack of approval from the Ethical and Research Committee.

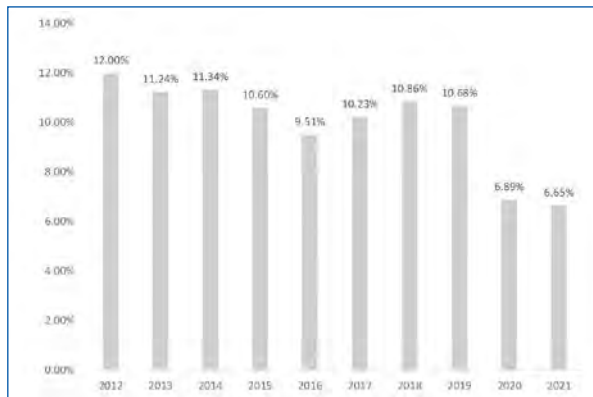


Figure 3. New leprosy cases in each year between 2012 and 2021 in Brasil.

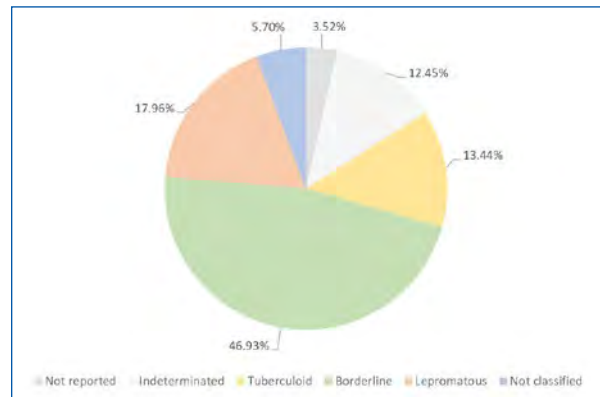


Figure 4. Madrid classification of leprosy, in Brasil, between 2012 and 2021.

Results

During the period between 2012 and 2021, 338,904 cases of leprosy were reported in Brasil. Most cases lived in the Northeast region (42.65%), followed by the Central-West region (20.12%), the North region (19.54%), the Southeast region (14.25%), and the South region (3.41%), respectively (Fig. 1). The Brazilian state with the highest number of cases was Maranhão, responsible for 28.10% of the cases in the Northeast region and 11.99% of the cases in the country (Fig. 2).

The year with the highest number of reported cases was 2012 (12%), followed by 2014 (11.34%) and 2013 (11.24%). The last year analyzed, 2021, was the one with the lowest number of cases so far (6.65%), followed by 2020 (6.89%) (Fig. 3).

Based on the WHO classification, 25.09% were classified as PB, 74.75% as MB, and 0.15% were not reported under any of these classes of leprosy. According to the Madrid classification, most cases were considered borderline leprosy (46.93%), 17.96% as lepromatous leprosy, 13.44% as tuberculoid leprosy, 12.45% as indeterminate leprosy, 5.7% were not classified, and in 3.52% the classification was not reported (Fig. 4).

Regarding gender, leprosy was observed more in men (56.93%) than in women (43.06%). In 0.01% of the cases, gender was not reported. Most patients (50.89%) had mixed ethnicities; 24.31% were Caucasian, 12.58% were Black, 0.94% were Asian, and 0.43% were Indian. Ethnicity was not reported in 3.86% of the compulsory notification forms.

Most patients had between 40 and 59 years (37.68%), followed by the age periods between 20 and 39 years (28.7%), 60 and 79 years (20.98%), 0 and 19 years old

(10.34%), and those aged 80 years or older (2.31%) (Fig. 5). Around 5.91% were between 0 and 14 years.

Most patients had incomplete elementary school (42.76%), 7.44% had completed elementary school, 6.24% had incomplete high school, 12.22% had completed high school, 1.38% had incomplete graduation, and 3.04% had completed graduation. A total of 9.08% of patients were illiterate (Fig. 6).

Regarding the MDT regimen, 73.32% of the patients were treated with 12 doses, 24.81% with six doses, and 1.57% were treated with alternative treatment regimens. This field was not completed in 0.3% of the compulsory notification forms.

In most cases, patients were considered healed and discharged for cure (70.65%). 5.83% abandoned the treatment; however, the number of these cases reduced progressively over the years, with 2021 having the lowest number of cases abandoning treatment (1.09%). Around 1.61% of cases died of leprosy, but 2021 was also the year with the lowest number of deaths (3.91%) (Fig. 7). A total of 1.51% of patients initially reported as having leprosy were later reclassified into other diseases.

In new cases, that is, patients with characteristic signs and symptoms but who have never received specific treatment⁷, predominated (81.02%) over recurrences (4.48%).

No leprosy reactions were documented in 60.66% of the cases, 9.71% evolved only with type 1 leprosy reaction, 3% evolved only with type 2 leprosy reaction, and 1.37% evolved with both types of leprosy reaction. This item was not completed in 25.27% of the notification forms.

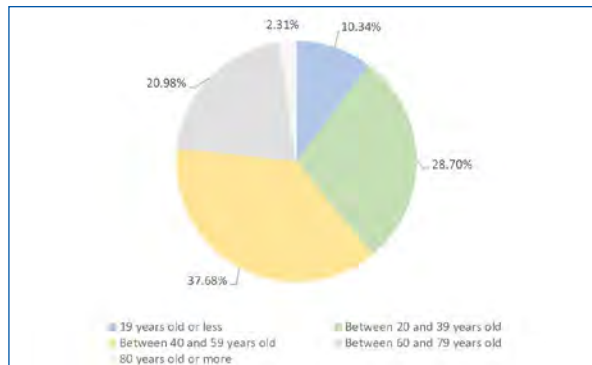


Figure 5. Age-group of leprosy cases, in Brasil, between 2012 and 2021.

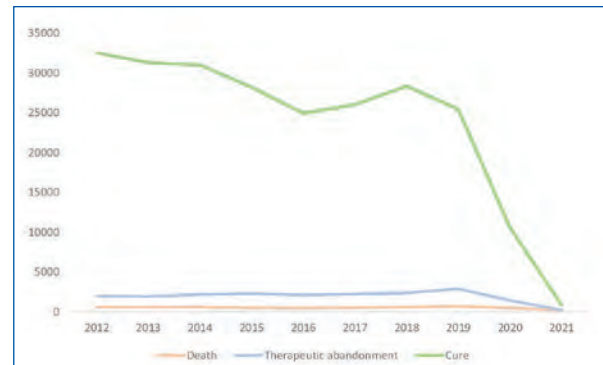


Figure 7. Patients who evolved to death, therapeutic abandonment, or cure between 2012 and 2021.

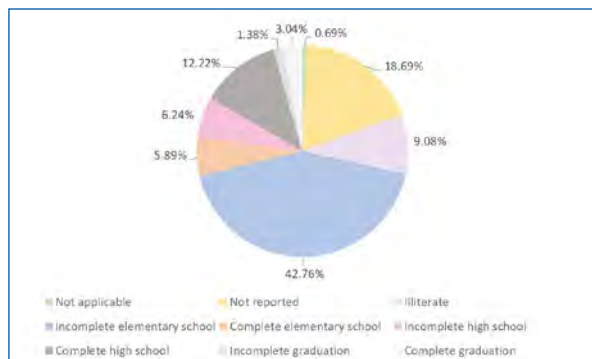


Figure 6. Educational level of leprosy cases, in Brasil, between 2012 and 2021.

Disability was graded as 0 (absence of neural involvement), grade 1 (decrease or loss of sensation in the eyes, hands, and feet), and grade 2 (serious injuries to the eyes, hands, and feet)^{7,8}, observed at the time of diagnosis, respectively in 54.78, 24.52, and 8.45%. Disabilities were not evaluated or not specified in the notification forms, respectively, in 4.46 and 7.76% of the cases.

Discussion

Leprosy is considered a neglected tropical disease. In the 1980s, after the introduction of MDT, there was a significant reduction in the number of cases⁵. However, Brasil has not yet managed to reach the level of elimination of disease, that is, a prevalence of less than one case per 10,000 inhabitants⁴.

Actions to reduce the burden of leprosy in the country continue to be influenced by the COVID-19 pandemic, with an impact on the diagnosis and monitoring of cases of the disease in Brasil. Although there has been a

decrease in leprosy cases over the years, the sharpest reduction in the last 2 years may be related to the lower detection of cases caused by the COVID-19 pandemic⁴, justified by the closure of health services intended for the diagnosis of Hansen's disease, as shown in Figure 3.

In the Brazilian scenario, the inequality observed in leprosy control is notorious. The Northeast region had more than twice as many cases compared to other regions. This may be associated with the fact that this region is considered the poorest in the country, with many inhabitants living in an unfavorable socioeconomic situation. The south and southeast regions showed a reduction in cases of leprosy. The large Brazilian territorial extension and socioeconomic inequalities are cited as the main reason for this discrepancy⁸⁻¹⁰. Maranhão was the state with the highest number of cases. The endemicity of leprosy in this state is related to low values in the Human Development Index, which challenges the control of the disease⁹.

The predominant type observed was MB disease, which is associated with late detection of the disease, contributes to maintaining transmissibility, and worsens neurological damage⁸.

Regarding gender, the fact that men seek health services less and that they are more prone to *Mycobacterium leprae* infection in their professional environment are factors for the greater number of cases in males⁸.

The educational level of most patients with leprosy was very low. The lower the level of education, the greater the probability of occurrence and reactivation of leprosy, as this class has a low level of knowledge and often less understanding of treatment guidelines, preventive measures, and forms of self-care^{9,11}. This educational deficit can also delay the diagnosis and perception of the emergence of complications of the disease¹¹. Social conditions and educational

vulnerability are associated with precarious situations of hygiene, poverty, and low socioeconomic status⁹.

Leprosy has a long incubation period, which is associated with the delay in diagnosis and initiation of treatment are factors for the increase in the number of cases with age progression, especially in economically active people, as shown above. The occurrence of leprosy in the age group under 15 years has a great epidemiological value, as it indicates an early exposure to the etiological agent, making it an important point for evaluating its transmissibility⁸.

Most cases progressed to cure. Adequate treatment is a key factor in curing the patient in order to interrupt the chain of transmissibility, thus being an important tool for controlling the disease. In addition, it plays a crucial role in preventing disabilities¹¹.

The main social impact of leprosy occurs due to the genesis of disabilities. The complications can be responsible for permanent sequelae, resulting in social and psychological damage¹¹. Most patients had grade 0 disability at the diagnosis moment. However, a considerable percentage of the patients were not evaluated for disabilities or not specified in notification forms.

Current leprosy control strategies rely on early diagnosis and prompt treatment to minimize the progressive morbidity of leprosy and hopefully interrupt transmission from clinically active cases³.

Conclusion

The limitation of this study was the impossibility of analyzing some information due to failures to fill in the SINAN forms.

Despite significant improvements in leprosy control in recent decades, the disease persists as a public health problem. Identifying behavioral and environmental risk factors for developing leprosy is a difficult task because of the long incubation time of the disease³. We emphasize the need to expand the field of leprosy research in order to understand its epidemiology in Brasil and have an early intervention to reduce late diagnoses and consequent physical disabilities.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Araújo MG. Hanseníase no Brasil. *Rev Soc Bras Med Trop*. 2003;36.
2. Fontes ANB, Lima LNGC, Mota RMS, Almeida RLF, Pontes MA, Gonçalves HS. Genotyping of *Mycobacterium leprae* for better understanding of leprosy transmission in Fortaleza, Northeastern Brasil. *PLOS Neglected Tropical Diseases*. 2017;11.
3. Avanzi C, Singh P, Truman RW, Suffys PN. Molecular epidemiology of leprosy: An update. *Infect Genet Evol*. 2020;86:104581.
4. Ministério da Saúde do Brasil M. Boletim Epidemiológico Hanseníase 2022. Boletim Epidemiológico de Hanseníase. 2022;Jan.
5. World Health Organization. Global leprosy strategy 2016-2020: accelerating towards a leprosy-free world [Internet]. New Delhi: World Health Organization; 2016 [cited 2018 Oct 19]. 20 p.
6. World Health Organization. Regional Office for Southeast Asia. (2018). Guidelines for the diagnosis, treatment and prevention of leprosy. World Health Organization. Regional Office for Southeast Asia. <https://apps.who.int/iris/handle/10665/274127>. Licença: CC BY-NC-SA 3.0 IGO
7. Li YY, Shakya S, Long H, Shen LF, Kuang YQ. Factors influencing leprosy incidence: a comprehensive analysis of observations in Wenshan of China, Nepal, and other global epidemic areas. *Front Public Health*. 2021;9:666307.
8. Lima Filho CA, Portugal WM, Silva AM, Araújo KMST, Albuquerque AOB, Silva MVB, et al. Epidemiological profile of leprosy in Northeastern Brasil in the period 2016 to 2020. *Res Soc Dev*. 2021;10:e529101523266.
9. Anjos LHG, Cunha SM da, Batista GM, Higino TMM, Souza DCP, Aliança ASS. Epidemiological profile of leprosy in the state of Maranhão from 2018 to 2020. *Res Soc Dev*. 2021;10(15):e272101523156.
10. Azevedo VM, Lacerda BS, Fecury AA. Panorama da hanseníase entre as macrorregiões brasileiras de 2015 a 2018. *Rev Cien Multi Núc do Com*. 2020;1:111-23.
11. Ribeiro GC, Félix Lana FC. Incapacidades físicas em hanseníase: caracterização, fatores relacionados e evolução. *Cogitare Enferm*. 2015;20:496-503.

Prevalence of four urogenital sexually transmitted infections in a dedicated clinic from Lisbon

Prevalência de quatro infeções sexualmente transmissíveis curáveis numa clínica especializada em Lisboa

Zohra Lodhia^{1,a}, Jacinta Azevedo^{2,b}, João Alves², Dora Cordeiro¹, Marília Antunes^{3,c}, and Maria J. Borrego^{1,d*}

¹National Reference Laboratory (NRL) for Sexually Transmitted Infections (STI), Instituto Nacional de Saúde Doutor Ricardo Jorge; ²Sexually Transmitted Diseases Clinic, Centro de Saúde da Lapa; ³Centro de Estatística e Aplicações, Faculdade de Ciências, Universidade de Lisboa. Lisbon, Portugal
ORCID: ^a0000-0002-9477-9646; ^b0000-0001-8904-5819; ^c0000-0002-1257-2829; ^d0000-0002-8604-8800

Abstract

Background/Objectives: To determine the prevalence of urogenital *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV), and *Mycoplasma genitalium* (MG) among attendees of an open and freely available sexually transmitted infections (STI) dedicated clinic in Lisbon, at Centro de Saúde da Lapa, during 1-year. **Methods:** Molecular testing for CT, NG, MG, and TV was performed on 1,062 urogenital specimens (one specimen per person). A descriptive, cross-sectional, observational study was conducted to evaluate the characteristics of infected persons. Statistical analysis was performed. **Results:** Around 237 infections were detected in 214 patients. CT was the most prevalent (11.6%), with a similar infection rate between men and women. NG was the second most frequently detected (7.3%), followed by MG and TV (2.9 and 0.5%, respectively). Statistically significant associations were found: 1) between younger age and CT and NG prevalence, where being < 25 years old constituted an increased risk factor; 2) between CT and NG prevalence and sexual orientation, where heterosexuals presented an increased risk for CT infections while men who have sex with men (MSM) had a higher risk for NG infections; and 3) between “having symptoms” and gonococcal infection. **Conclusions:** This study highlights the rising of CT and NG in contrast to a low rate of MG and to the scarceness of TV.

Keywords: Sexually transmitted infections. *Trichomonas vaginalis*. *Neisseria gonorrhoeae*. *Chlamydia trachomatis*. *Mycoplasma genitalium*.

Resumo

Fundamentos/Objetivos: Determinar a prevalência das infeções urogenitais por *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV) e *Mycoplasma genitalium* (MG) nos utentes duma clínica de infeções sexualmente transmissíveis (IST), aberta e gratuita, localizada em Lisboa, no Centro de Saúde da Lapa, durante 1 ano. **Métodos:** A pesquisa de CT, NG, MG e TV foi realizada por teste de amplificação génica em 1062 espécimes urogenitais (1 amostra por pessoa). Foi efetuado um estudo descritivo, transversal e observacional das pessoas infetadas. Foi realizada análise estatística. **Resultados:** Foram detetadas 237 infeções em 214 utentes. CT foi a IST mais prevalente (11,6%), com

*Correspondence:

Maria J. Borrego

E-mail: m.jose.borrego@insa.min-saude.pt

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taxa de infecção similar em homens e mulheres. Seguidamente NG (7,3%), MG (2,9%) e TV (0,5%). Foram encontradas associações estatisticamente significativas: 1) entre idade e prevalência de CT e NG, sendo a idade < 25 anos um fator de risco acrescido; 2) entre prevalência de CT e NG e orientação sexual, mediante a qual os heterossexuais apresentaram risco aumentado para CT e os homens que têm sexo com homens um risco aumentado para NG; e, 3) entre 'sintomas' e infecção gonocócica. **Conclusões:** Este estudo evidencia uma subida da prevalência das infeções por CT e NG em contraste com uma baixa taxa de infecção por MG e um escasso número de casos de TV.

Palavras-chave: Sexually transmitted infections. *Trichomonas vaginalis*. *Mycoplasma genitalium*. *Neisseria gonorrhoeae*. *Chlamydia trachomatis*.

Introduction

The World Health Organization estimates that > 1 million STIs are acquired everyday worldwide, leading to 376 million cases of *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Treponema pallidum* (TP), and TV every year¹. Population-based studies estimate 1-3% the rate of *Mycoplasma genitalium* (MG) infection in sexually active men and women², and that coinfection with CT and/or NG is not uncommon³. MSM, intravenous drug users, people who have multiple sexual partners, adolescents, and young adults aged between 15 and 24 years old account for the majority of the STI cases, although TV prevalence rates peak at 40-50 years old².

The most predominant CT and NG symptoms are related to urogenital infections, namely urethritis and epididymitis in men and cervicitis and pelvic inflammatory disease in women. However, because most STIs are frequently asymptomatic, people do not realize they are infected and, accordingly, fail to seek treatment, which may lead to severe complications, namely tubal infertility in women³.

In Portugal, there is a lack of data regarding the prevalence of CT, NG, MG, and TV. Therefore, the present work aims to determine the frequency of these four curable urogenital STIs among attendees of an open and free STI clinic located in Lisbon and to evaluate their characteristics.

Methods

We conducted a descriptive, cross-sectional, observational study, reviewing medical charts from all individuals attending the open and freely available STI clinic (no limitations related to residence area, nationality, or legal status) located in Lisbon, Portugal ("Consulta de DST Lapa", ARSLVT, IP). The "Consulta de DST Lapa" has been operating since 1987, being the only STI clinic in a primary healthcare facility in the country. All attendees (with or without genital symptoms, either due to a new problem or through patient referral) are systematically

screened for human immunodeficiency virus (HIV) and TP through serological testing and for CT and NG in urine and/or urethral and endocervical samples. Additional molecular screening for CT and NG at the oropharynx and rectum, and for MG, TV and herpes simplex virus, are regularly performed according to the patient's clinical presentation. Genital warts are diagnosed through clinical observation.

For the purposes of the present study, during a 1-year study period, between September 2016 and November 2017, demographic and clinical information such as age, gender, sexual orientation, number of sexual partners in the previous 6 months, symptoms, concurrent and previous STI, and HIV status were collected and introduced in an anonymized database for further analysis. A total of 1,062 urogenital samples (97 endocervical or urethral swabs and 965 first-void urines—in general, urethral and endocervical swabs in symptomatic and urines in asymptomatic) were collected from all attendees (one-sample per person) and sent to the National Reference Laboratory for STI at the National Institute of Health (Instituto Nacional de Saude Doutor Ricardo Jorge, INSA, IP) for routine diagnosis by Cobas® 4800 CT/NG (Roche Diagnostics). This test was performed according to the manufacturer's instructions. All eluates from Cobas® 4800 CT/NG testing were further systematically tested by the S-DiaMGTV™ kit (Diagenode S.A.) for MG/TV, according to the manufacturer's instructions.

From the collected samples, 746 (70.2%) were from men and 316 (29.8%) from women. For analysis purposes, we created two groups according to age: "< 25 years old" (n = 234, 22.0%) and "≥ 25 years old" (n = 828, 78.0%). Regarding sexual orientation, four groups were defined—"heterosexual men" (n = 391, 36.8%), "heterosexual women" (n = 301, 28.3%), "MSM" (n = 355, 33.4%), and "women who have sex with women (WSW)" (n = 15, 1.4%).

Attendees were further grouped into "no symptoms" (607, 57.1%), "symptoms", which only included "discharge and/or dysuria" (n = 186, 17.5%), and "other symptoms"

Table 1. Sociodemographic characteristics and sexual behavior of the STI clinic attendees

	Men (746/1,062)	Women (316/1,062)	Total study population
Age			
< 25 (n,%)	138 (18.5)	96 (30.1)	234 (22.0)
≥ 25 (n,%)	608 (81.5)	220 (69.6)	828 (78.0)
Sexual orientation			
Heterosexual (n,%)	391 (52.4)	301 (95.3)	692 (65.2)
MSM/WSW (n,%)	355 (47.6)	15 (4.7)	370 (34.8)
Number of sexual partners			
0 (n, %)	23 (3.1)	15 (4.7)	38 (3.6)
1 (n, %)	193 (25.9)	161 (50.9)	354 (33.3)
2-4 (n, %)	385 (51.6)	122 (38.6)	507 (47.7)
5+ (n, %)	144 (19.3)	18 (5.7)	162 (15.3)
Symptoms			
No symptoms (n, %)	403 (54.0)	204 (64.6)	607 (57.1)
Discharge and/or dysuria (n, %)	130 (17.4)	56 (17.7)	186 (17.5)
Other* (n, %)	218 (29.2)	57 (18.0)	275 (25.9)
Previous STI			
CT (n, %)	67 (9.0)	27 (8.5)	94 (8.9)
NG (n, %)	92 (12.3)	13 (4.1)	105 (9.9)
MG (n, %)	1 (0.1)	0 (0.0)	1 (0.1)
TV (n, %)	0 (0.0)	3 (0.9)	3 (0.3)
HIV			
Positive (n, %)	70 (9.4)	4 (1.3)	74 (7.0)
Negative (n, %)	676 (90.6)	312 (98.7)	988 (93.0)

*Other includes ulcers/erosions, genital warts, or non-STI symptoms with the genital expression.

(n = 275, 25.9%). For analysis purposes, only “discharge and/or dysuria” was considered as these were the ones directly associated with CT, NG, MG, and TV.

Table 1 summarizes the characteristics of the study population.

The association between the categorical variables concerning potential risk factors and the outcomes of interest was assessed through the Chi-squared test of independence. The odds ratio (OR) and the correspondent 95% confidence intervals (CI) were calculated using a simple logistic regression model (LRM). In these cases, the choice of the reference category of the risk factor (independent variable in the LRM) was made such that the OR would quantify the eventual excess (or shortage) of risk associated with the category a priori thought of as the most interesting, based on the literature (the reference category would be one of the lower reported risks in the literature)^{3,4}. Whenever the value “one” does not belong to the 95% CI, it means that the hypothesis OR = 1 is rejected at a 5%

significance level, and hence a significant association is found between the exposure to the risk factor and the occurrence of the disease (outcome). Differences with a p-value of < 0.05 were considered statistically significant. Statistical analysis was performed using software R (4.0.2) and Rstudio (version 1.3.1093). Whenever the number of cases was low, only descriptive statistics were performed.

Results

Around 237 urogenital STIs were detected in 214 patients, while the remaining 848 attendees tested negative for the four STIs under evaluation. CT was the most prevalent STI, with 11.6% (123/1,062) and a similar infection rate between men (85/746, 11.4%) and women (38/316, 12.0%). NG was the second most frequently detected STI, with 7.3% (78/1,062), followed by MG and TV, with 2.9% (31/1,062) and 0.5% (5/1,062), respectively (Fig. 1). Probably due to the low number

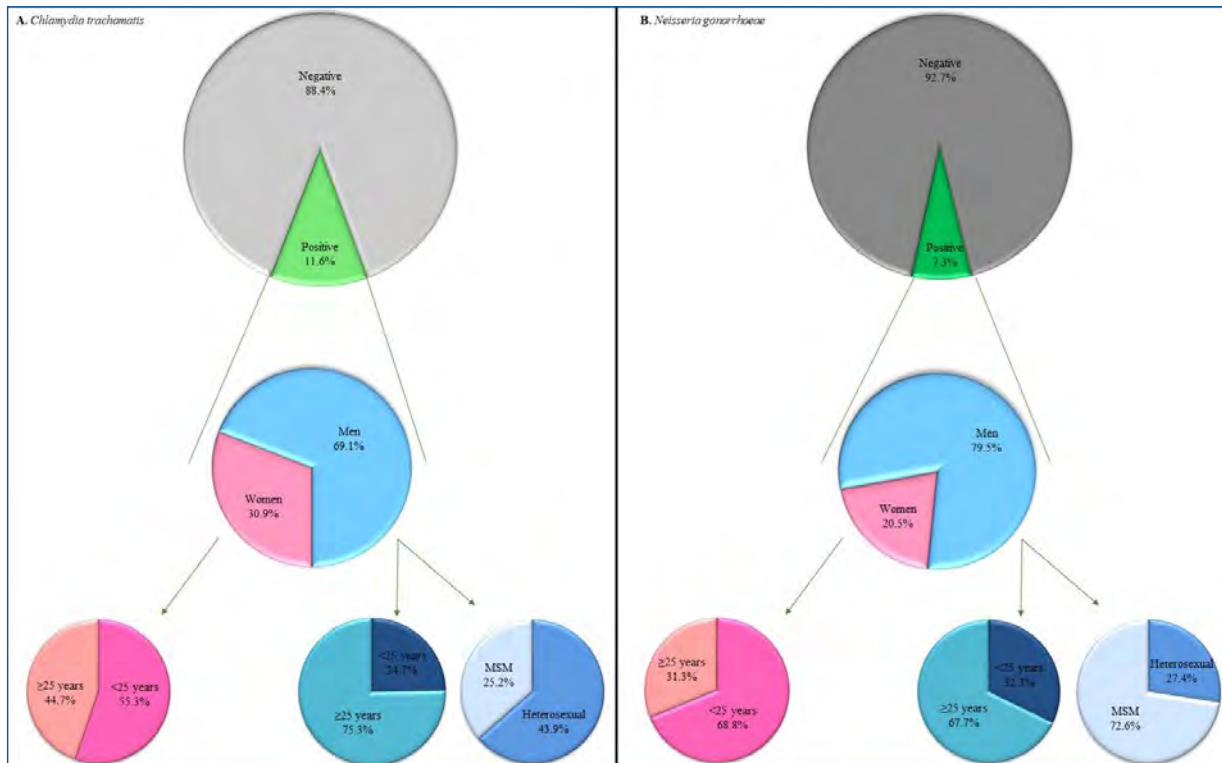


Figure 1. A: *Chlamydia trachomatis*; **B:** *Neisseria gonorrhoeae* infections in “Consulta de DST Lapa”: % of positives in the total population, in men (heterosexual and MSM) and women, and in < 25 and ≥ 25 years old.

of cases, no statistically significant association was found between TV infection and any of the variables.

Table 2 describes positive cases for any of the four STIs under study regarding gender, age, sexual orientation, number of sexual partners, symptoms, and HIV status.

Regarding gender, for every infection except NG, the odds of infection for women were slightly higher than for men (OR estimates consistently higher than one). For NG, the opposite was observed (Table 2).

We have detected that there was a statistically significant association between age and STI, except for MG; accordingly, being “< 25 years old” old constituted an increased risk factor for both CT and NG infections. A statistically significant association could also be established between STI and sexual orientation, namely with “heterosexual men” and “heterosexual women” presenting an increased risk for CT infections and “MSM” for NG infections (p-value of < 0.01 and 0.01, respectively). In both cases (age and sexual orientation), the odds of infection were more than duplicated when compared to the reference group (OR = 2.07 and 2.87 for age; OR = 2.22 and 2.31 for sexual orientation) (Table 2).

The number of sexual partners was statistically associated with having any of the four STIs (p-value = 0.03), but there was no specific association with CT, NG, or MG. However, having more than one sexual partner during the last 6 months constituted an increased risk factor for presenting any of the four STIs (Table 2).

The prevalence of coinfections among the STI clinic attendees was 2.0% (21/1,062): 14 CT/NG, 3 CT/MG, 1 CT/TV, 1 NG/MG, 1 CT/NG/TV, and 1 CT/NG/MG. A statistically significant association was observed between being simultaneously CT positive and NG positive (p-value = 0.01), and patients who are NG positive have increased odds for infection by CT (OR = 2.43). From 237 patients diagnosed with any of the four STIs, 51 previously had CT (n = 33) and/or NG (n = 36), being there a statistically significant association and increased odds of infection between having any of the four STI and having had previously one of the same four STI (p-value of < 0.01, OR = 2.07). Also, being NG positive and having previously had any of the four STIs were associated (p-value of < 0.01) with increased odds of gonococcal infection when patients had previously had one of those four STIs in their clinical history (OR = 2.08).

Table 2. STI cases by gender, age group, sexual orientation, number of sexual partners, symptoms, and HIV status

	Any of the four STI (237/1,062)	<i>Chlamydia trachomatis</i> (123/1,062)	<i>Neisseria gonorrhoeae</i> (78/1,062)	<i>Mycoplasma genitalium</i> (31/1,062)	<i>Trichomonas vaginalis</i> (5/1,062)
Gender					
Men (n + /n, %)	156/746 (19.6)*	85/746 (11.4)*	62/746 (8.3)	21/746 (2.8)*	1/746 (0.1)
Women (n + /n, %)	58/316 (18.4)	38/316 (12.0)	16/316 (5.1)*	10/316 (3.2)	4/316 (1.3)
χ^2	0.03	0.70	0.23	0.05	a
p-value	0.87	0.40	0.63	0.82	a
OR (95% CI)	1.04 (0.74, 1.46)	1.22 (0.80, 1.84)	1.20 (0.68, 2.23)	1.19 (0.53, 2.51)	a
Age					
< 25 (n + /n, %)	78/234 (33.3)	42/234 (17.9)	31/234 (13.2)	10/234 (4.3)	1/234 (0.4)
≥ 25 (n + /n, %)	136/828 (16.4)*	81/828 (9.8)*	47/828 (5.7)*	21/828 (2.5)*	4/828 (0.5)
χ^2	27.44	11.10	15.13	0.18	a
p-value	<< 0.01	<< 0.01	<< 0.01	0.67	a
OR (95% CI)	2.49 (1.76, 3.49)	2.07 (1.35, 3.13)	2.87 (1.68, 4.86)	1.31 (0.54, 2.88)	a
Sexual orientation					
Heterosexual (n + /n, %)	76/391 (19.4)*	54/391 (13.8)	17/391 (4.3)*	9/391 (2.3)	1/391 (0.3)
MSM (n + /n, %)	80/355 (22.5)	31/355 (8.7)*	45/355 (12.7)	12/355 (3.4)*	0/355 (0.0)
χ^2	0.42	8.90	6.16	0.19	a
p-value	0.51	< 0.01	0.01	0.65	a
OR (95% CI)	0.87 (0.59, 1.26)	2.22 (1.34, 3.77)	2.31 (1.24, 4.48)	0.74 (0.29, 1.81)	a
Number of sexual partners					
0-1 (n + /n, %)	61/392 (15.6)*	37/392 (9.4)*	19/392 (4.8)*	9/392 (2.3)*	1/392 (0.3)
2+ (n + /n, %)	153/669 (22.9)	86/669 (12.9)	59/669 (8.8)	22/669 (3.3)	4/669 (0.6)
χ^2	4.62	1.74	1.27	1.01	a
p-value	0.03	0.19	0.26	0.31	a
OR (95% CI)	1.47 (1.05, 2.07)	1.36 (0.90, 2.08)	1.44 (0.8, 2.59)	1.64 (0.75, 3.96)	a
Symptoms					
No symptoms (n + /n, %)	93/607 (15.3)	64/607 (10.5)	19/607 (3.1)*	13/607 (2.1)	5/607 (0.8)
Symptoms (discharge and/or dysuria) (n + /n, %)	99/186 (53.2)*	44/186 (23.7)*	57/186 (30.6)	13/186 (7.0)*	0/186 (0.0)
χ^2	116.31	20.25	141.25	12.97	a
p-value	<< 0.01	<< 0.01	<< 0.01	< 0.01	a
OR (95% CI)	0.16 (0.11, 0.23)	0.37 (0.24, 0.58)	17.66 (9.90, 33.02)	0.26 (0.12, 0.55)	a

*Reference group: a, no statistics were performed due to a low number of cases. Each cell of Table 2 should be read as the number of positive cases in each category, regarding the total number of cases for that same variable in the category, and the respective percentage. E.g., the information concerning variable gender regarding CT infection should be read as 85 out of the total 746 men are positive for CT; which means that 11.4% of men are infected with CT; 38 out of the 316 women are positive for CT; meaning that 12.0% of women are infected with CT. Chi-squared test statistic for independence between gender and infection by CT is equal to 0.7, to which a p-value of 0.4 is associated; OR of infection by CT is of 1.22, with a 95% CI equal to (0.80, 1.84), meaning that the odds of infection by CT is estimated to be 1.22 higher among women than in among men (reference category); hypothesis that OR = 1 is not rejected at a 0.05 significance level, as one belongs to the 95% CI.

Concerning the existence of “symptoms”, there was a very high-risk of infection associated (OR = 1 7.70) and a strong statistically significant association between the presence of “discharge and/or dysuria” and gonococcal infection (p-value of << 0.01) (Table 2).

Having any of the four STIs under study and HIV status and syphilis provided no statistically significant association (p-value = 0.70 and 0.13, respectively).

Discussion

A fifth of the STI clinic attendees (n = 214, 20.2%) were diagnosed with at least one of the four curable urogenital STIs (CT, NG, MG, and TV), and the most frequent was CT (11.6%) (Fig. 1) and (Table 2), as expected, according to the literature⁵⁻⁸.

In 2014, a national system for the epidemiological surveillance of obligatory reporting diseases, including

CT, was implemented in Portugal. In the early years, it was based on clinical notification, and since 2017, it includes both clinical and laboratory notification (<https://sinave.min-saude.pt/>). Thus, the Portuguese history of CT infection was short by the start of our study. However, prior data from this same STI clinic evidenced lower prevalence rates, namely 8.4% between 2000 and 2007⁹, and 6.0% among HIV-infected patients during the 2009-2013 period¹⁰; thus, CT seems to be on the rise. This putative growth is particularly striking when our study was mostly based on urine samples (only 97 endocervical or urethral swabs from symptomatic patients), which are not considered ideal for CT diagnosis in asymptomatic women because of its lower sensitivity compared to endocervical (or vaginal) swabs²; as such, some chlamydial (and even gonococcal) infections might have remained undiagnosed in women.

Neisseria gonorrhoeae (NG) has been under surveillance in our country since the 1950s, but its large under-reporting is common knowledge. It was the second most frequent STI in the present study with a prevalence of 7.3% (Fig. 1 and Table 2), a rise from the 3.1% determined during the 1998 and 2006 period (data not shown), and contrasting to the 1.3% positivity rate determined by a Netherlander study⁶ held in a similar clinical setting. The reasons underlying this rise are hard to determine. Increased risky behaviors related to preexposure prophylaxis (PrEP) for HIV could be implicated, as proposed by other studies reporting higher rates in those patients¹¹; however, this should not be the case in our study, as PrEP was only approved by Portuguese health authorities later in 2018. Our findings reinforce the need for continuous surveillance of gonorrhea dissemination because of the risk of antimicrobial-resistant strains, which have been described in our country¹², and the putative risk of treatment failure.

Regarding MG, an STI that is not under surveillance in Portugal nor in other European countries, its prevalence was 2.9%, which is lower than the described for similar clinics in other countries. In fact, several European studies^{6,13-15}, evidenced percentages varying from 3.0 to 9.8%, and it surely contrasts with the obtained in similar clinical settings in the United States (16.1% for women and 17.2% for men) and Canada (7.2% for women and 5.3% for men)^{16,17}. In fact, the observed 2.9% MG rate is similar to the described for low-risk populations (2.0%)⁶; considering that the demographic and behavioral risk factors for this infection are shared with CT and NG¹⁸, it would be expected that the high percentages detected for the later infections would be reflected for MG too. The reasons underlying this low rate are hard to determine but are

consistent with previous data from the “Consulta de DST Lapa” (data not shown), in which this microorganism was rarely detected; thus, specificities of the Portuguese MG epidemiological scenario, putatively evidenced by our study, require disclosure.

Trichomonas vaginalis (TV) is not under surveillance in Portugal, similar to most countries. The “Consulta de DST Lapa” has been observing a decline in TV since the 90s, and the present prevalence of 0.5%, the lowest of the four curable STIs under evaluation, was not a complete surprise. In addition, it is in accordance with a prevalence ranging between 0.6 and 1.5% described for Netherlander and French STI clinics^{6,13}. It is of note that, in our study, men represented about two-thirds of the population, and men are usually considered less prone to TV infection. Nonetheless, a study involving Portuguese women of childbearing age somehow corroborates our findings, as a 1.0% prevalence rate was determined¹⁹. On the contrary, in Iran, a study performed in STI clinics only involving women reported that the overall TV prevalence was 8.3%⁸, and in North America, incarcerated people prevalence rates varied between 2 and 47%²⁰. Thus, the TV prevalence outside Europe may not parallel the European situation. The impact of a putative indiscriminate use of vaginal antiseptics or vaginosis therapeutics could be contributing to the apparent disappearance of the protozoan; further evaluation of this phenomenon is needed.

Previous studies showed that some variables such as age, gender, concurrent STI, and/or number of sexual partners constitute risk factors for acquiring a new STI³ and, in general, women were considered more prone to getting an STI²¹. However, in our study, the most obvious association was NG infection with men as described by others⁴.

Sexually transmitted infections (STI) were expected to be associated with young age²¹; in fact, ectocervical everted columnar epithelium that characterizes women of young age should contribute to a high-risk of acquiring an STI²². As such, in our study, being “< 25 years old” constituted an increased risk factor for both CT (p-value of << 0.01, OR = 2.07) and NG (p-value of << 0.01, OR = 2.87). This is of great concern, as nontreated infections can ascend to the upper genital tract and cause pelvic inflammatory disease and related sequelae²³. For MG, and in line with the described by others^{13,14}, no such association was observed; in our study, older people presented an increased risk for MG infection (OR = 1.31).

Concerning the association between urogenital STI and sexual orientation, being “heterosexual” constituted an increased risk for CT infection (p-value of < 0.01), while being “MSM” constituted an increased risk for NG

infection (p-value = 0.01), which is in accordance with other studies²¹. Although no association could be established between MG and sexual orientation, the odds in MSM were slightly higher (Table 2), corroborating the results of a Spanish study²⁴.

Having multiple sexual partners has been often associated with an increased risk of acquiring and transmitting STIs^{18,21}. Accordingly, more than half of our patients (n = 669 and 63.0%) reported having more than one sexual partner during the last 6 months.

Considering that the only symptom that was recorded, for analysis purposes, was “discharge and/or dysuria”, 82.5% of attendees were considered asymptomatic, a feature that was statistically significantly associated, p-value << 0.01 and < 0.01, with CT and MG, respectively. On the contrary, “having symptoms” and NG were statistically significantly associated, evidencing very high odds of infection when compared to “not having symptoms” (OR = 17.66). However, if only patients who had symptoms were tested, many NG cases would have been missed; therefore, a generalized screening accompanied by appropriate treatment should surely contribute to reducing the NG reservoir in high-prevalence communities.

Regarding having had at least one of the four STIs previously, despite the development of some immunity upon suffering several STI episodes, it does not provide enough protection against the acquisition of a new STI²⁵. As such, almost one-fifth of our study population (n = 182, 17.1%) had at least one of the four STIs in the past, and 28.6% (n = 52) of the people from this group had also an STI in the present. Constant reinfections evidence lack of use of preventive methods and repeated high-risk behaviors, which should also facilitate acquisition and transmission of HIV²⁶; nonetheless, no statistically significant association was observed between having any of the four curable STIs under study and being HIV positive.

This study presents some limitations regarding the anatomical sites of infection-as it only included urogenital samples. Also, regarding symptoms, only “discharge and/or dysuria” were systematically recorded, missing potential curable STI-related symptoms such as itching and pelvic pain. Nonetheless, it contributes to fulfilling the lack of data on the prevalence of CT, NG, MG, and TV in Portugal, evidencing that among STI clinic attendees in Lisbon, Portugal, TV reveals rare, MG occasional, and NG and CT on the rise. NG was associated with being MSM, being young, and having discharge. CT was the most prevalent STI and was associated with being “heterosexual men” and being “< 25 years old”.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

- Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ. 2019;97:548-62P.
- Unemo M, Ballard R, Ison C, Lewis D, Ndowa F, Peeling R. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. World Health Organization. 2013. Available from: apps.who.int/iris/handle/10665/85343.
- Workowski KA, Bolan GA; Centers for Disease Control and Prevention; Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1-137.
- European Centre for Disease Prevention and Control. Gonorrhoea. In: ECDC. Annual epidemiological report for 2018. Stockholm: ECDC; 2020.
- Banerjee P, Thorley N, Radcliffe K. A service evaluation comparing home-based testing to clinic-based testing for chlamydia and gonorrhoea in Birmingham and Solihull. Int J STD AIDS. 2018;29:974-9.
- de Jong AS, Rahamat-Langendoen JC, van Alphen P, Hilt N, van Herk C, Pont S, et al. Large two-centre study into the prevalence of *Mycoplasma genitalium* and *Trichomonas vaginalis* in the Netherlands. Int J STD AIDS. 2015;27:856-60.
- Clarivet B, Picot E, Marchandin H, Tribout V, Rachedi N, Schwartzentruber E, et al. Prevalence of Chlamydia trachomatis, *Neisseria gonorrhoeae* and *Mycoplasma genitalium* in asymptomatic patients under 30 years of age screened in a French sexually transmitted infections clinic. Eur J Dermatol. 2014;24:611-6.
- Rajabpour M, Emamie AD, Pourmand MR, Goodarzi NN, Asbagh FA, Whitley DM. Chlamydia trachomatis, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* among women with genitourinary infection and pregnancy-related complications in Tehran: A cross-sectional study. Int J STD AIDS. 2020;31:773-80.
- Santo I, Azevedo J, Nunes B, Gomes JP, Borrego MJ. Partner notification for Chlamydia trachomatis urogenital infections: eight years of patient referral experience in the major Portuguese sexually transmitted infections clinic, 2000-07. Int J STD AIDS. 2011;22:548-51.
- Azevedo T, Brasileiro A, Borges F, Mansinho K, Santo I, Azevedo J. High Incidence of Sexually Transmitted Infections in Patients with HIV-Infection. SPDV [Internet]. 2017 Apr.17 [cited 2023Apr.17]; 75(1):59-3. Available from: <https://revista.spdv.com.pt/index.php/spdv/article/view/719>
- Nguyen VK, Greenwald ZR, Trottier H, Cadieux M, Goyette A, Beauchemin M, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS. 2018;32:523-30.
- Pinto M, Matias R, Rodrigues JC, Duarte S, Vieira L, Gonçalves I, et al. Cephalosporin-resistant *Neisseria gonorrhoeae* isolated in Portugal, 2019. Sex Transm Dis. 2020;47:e54-6.

13. Pereyre S, Laurier Nadalié C, Bébéar C investigator group. *Mycoplasma genitalium* and *Trichomonas vaginalis* in France: a point prevalence study in people screened for sexually transmitted diseases. *Clin Microbiol Infect*. 2017;23:122.e1-7.
14. Svenstrup HF, Dave SS, Carder C, Grant P, Morris-Jones S, Kidd M, et al. A cross-sectional study of *Mycoplasma genitalium* infection and correlates in women undergoing population-based screening or clinic-based testing for *Chlamydia* infection in London. *BMJ Open*. 2014;4:e003947.
15. Hokynar K, Hiltunen-Back E, Mannonen L, Puolakkainen M. Prevalence of *Mycoplasma genitalium* and mutations associated with macrolide and fluoroquinolone resistance in Finland. *Int J STD AIDS*. 2018;29:904-7.
16. Getman D, Jiang A, O'Donnell M, Cohen S. *Mycoplasma genitalium* prevalence, coinfection, and macrolide antibiotic resistance frequency in a multi-center clinical study cohort in the United States. *J Clin Microbiol*. 2016;54:2278-83.
17. Gratrix J, Plitt S, Turnbull L, Smyczek P, Brandley J, Scarrott R, et al. Prevalence and antibiotic resistance of *Mycoplasma genitalium* among STI clinic attendees in Western Canada: a cross-sectional analysis. *BMJ Open*. 2017;7:e016300.
18. Lillis RA, Martin DH, Nsuami MJ. *Mycoplasma genitalium* infections in women attending a sexually transmitted disease clinic in New Orleans. *Clin Infect Dis*. 2019;69:459-65.
19. Silva J, Cerqueira F, Teixeira AL, Campainha R, Amorim J, Medeiros R. Prevalence of *Neisseria gonorrhoeae* and *Trichomonas vaginalis* in Portuguese women of childbearing age. *J Obstet Gynaecol*. 2021;41:254-8.
20. Meites E, Gaydos CA, Hobbs MM, Kissinger P, Nyirjesy P, Schwabke JR, et al. A review of evidence-based care of symptomatic trichomoniasis and asymptomatic *Trichomonas vaginalis* infections. *Clin Infect Dis*. 2015;61:S837-48.
21. de Coul EL, Warning TD, Koedijk FD Dutch, STI clinics, Sexual behaviour and sexually transmitted infections in sexually transmitted infection clinic attendees in the Netherlands, 2007-2011. *Int J STD AIDS*. 2014;25:40-51.
22. Tilson EC, Sanchez V, Ford CL, Smurzynski M, Leone PA, Fox KK, et al. Barriers to asymptomatic screening and other STD services for adolescents and young adults: focus group discussions. *BMC Public Health*. 2004;4:21.
23. Currie MJ, Bowden FJ. The importance of chlamydial infections in obstetrics and gynaecology: an update. *Aust N Z J Obstet Gynaecol*. 2007;47:2-8.
24. Fernández-Huerta M, Barberá MJ, Esperalba J, Fernandez-Naval C, Vall-Mayans M, Arando M, et al. Prevalence of *Mycoplasma genitalium* and macrolide resistance among asymptomatic people visiting a point of care service for rapid STI screening: a cross-sectional study. *Sex Transm Infect*. 2020;96:300-5.
25. Geisler WM, Lensing SY, Press CG, Hook EW 3rd. Spontaneous resolution of genital *Chlamydia trachomatis* infection in women and protection from reinfection. *J Infect Dis*. 2013;207:1850-6.
26. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. *J Acquir Immune Defic Syndr*. 2010;53:537-43.

Skin-related neglected tropical diseases in Angola: a retrospective analysis

Doenças tropicais negligenciadas relacionadas à pele em Angola: uma análise retrospectiva

Lídia P. Almeida-Voumard^{1,a*}, Cecília C. Almeida², Ernesto Afonso², Clarry N. Luvualu², José M. Pedro³, Maiza R. Baptista^{4,b}, Pascoal O. Alberto^{4,c}, Juliano V. Isaías⁴, and Christian F. Voumard²

¹Faculty of Medicine, Agostinho Neto University, Luanda; ²National Directorate of Public Health, Ministry of Health, Luanda; ³Provincial Health Delegation, Huambo; ⁴Dermatology Service, Américo Boavida Hospital, Luanda. Angola
ORCID: ^a0009-0009-8924-029X; ^b0009-0008-8976-7502; ^c0009-0005-2243-0532

Abstract

Objective: This was a retrospective analysis of the epidemiological and clinical profile of ten main skin neglected tropical diseases (NTDs) and appraisal of the role of dermatologists in the control and elimination of those diseases. **Methods:** Analysis of routine data and special investigations carried out by the Ministry of Health between 2017 and 2021, and internet search of published information on skin NTDs in Angola. **Results:** Except for yaws, all skin NTDs under review remain endemic. Previously unknown foci of Buruli ulcer (BU), cutaneous leishmaniasis (CL), and guinea worm disease (GWD) were detected in recent years. Leprosy, onchocerciasis, lymphatic filariasis, scabies, and snake bites are endemic countrywide. Weak laboratory services are a major constraint to confirm clinically suspected cases. The growing collaboration between public health workers, family doctors, and dermatologists is strengthening integrated approaches in NTDs control and elimination programs. **Conclusions:** The elimination of leprosy, BU, CL, and GWD as public health problems does not warrant the total interruption of their transmission chain over time. Effective case diagnosis and epidemiological surveillance are key strategies to control and eliminate skin NTDs. In addition to patient centered disease diagnosis and management, dermatologists must actively support field investigations, innovative training programs, and advocacy on skin NTDs.

Keywords: Angola. Skin-related neglected tropical diseases. Dermatology. Health services. Epidemiology.

Resumo

Objetivo: Análise retrospectiva do perfil epidemiológico e clínico de dez principais Doenças Tropicais Negligenciadas (DTNs) cutâneas e avaliação do papel do dermatologista no controle e eliminação dessas doenças. **Método:** Análise dos dados de rotina e investigações especiais realizadas pelo Ministério da Saúde entre 2017 e 2021, e busca na internet das publicações efectuadas sobre as DTNs cutâneas em Angola. **Resultados:** Salvo o pian (ou yaws), todas as DTNs consideradas no estudo permanecem endêmicas no país. Focos previamente desconhecidos de úlcera de Buruli (UB), leishmaniose cutânea (LC) e doença do verme da Guiné (DVG) foram detectados nos últimos anos. A hanseníase, a oncocercose, a filariose linfática, a

*Correspondence:

Lídia P. Almeida-Voumard

E-mail: lidiaavoumard2003@yahoo.fr

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sarna e as picadas de serpentes são endêmicas em todo o país. Fracos serviços de laboratório constituem uma grande limitação para confirmar casos clinicamente suspeitos. A crescente colaboração entre profissionais de saúde pública, médicos de família e dermatologistas fortalece abordagens integradas nos programas de controle e eliminação de DTNs.

Conclusões: A eliminação da hanseníase, da UB, da LC e da DVG como problemas de saúde pública não garante a interrupção total de sua cadeia de transmissão ao longo do tempo. O diagnóstico acertado dos casos e a vigilância epidemiológica são estratégias chaves para controlar e eliminar as DTN cutâneas. Além do diagnóstico e tratamento das DTNs centrados no paciente, os dermatologistas devem apoiar mais activamente a advocacia, as investigações de campo, e os programas de formação inovadores em DTNs cutâneas.

Palavras-chave: Angola. Doenças tropicais negligenciadas relacionadas com a pele. Dermatologia. Serviços de saúde. Epidemiologia.

Introduction

Skin-related neglected tropical diseases (NTDs) remain a major public health challenge in Angola, prevailing in poor social settings with reduced access to healthcare, education, water, and sanitation services. Information on these infectious diseases is scarce and fragmented, calling for a knowledge review on their epidemiological and clinical dimensions to better identify corrective measures regarding case detection, control, and elimination strategies¹⁻³.

Angola is a large country, with an area of 1,246,700 km², divided into 18 provinces and 164 municipalities, located on the South Atlantic coast of West Africa, between Congo and Namibia, bordering the Democratic Republic of Congo (DR Congo) and Zambia to the east. Population estimate was 33.9 million in 2021, including 46% of children aged 0-14 years; an estimated 45% of people had access to health services and 42% to potable water in 2018³.

The objective of this review is to document and analyze data collected from 2017 to 2021 by Ministry of health (MOH) as well as published information on the status of ten main skin-related NTDs.

Another purpose is to highlight the current and potential contribution of Angolan dermatologists to clinical, epidemiological, and educational activities to public health programs related to skin NTDs.

Methods

The following ten skin NTDs were included in the review: leprosy (Hansen's disease); lymphatic filariasis (LF); onchocerciasis; guinea worm disease (GWD or dracunculiasis); cutaneous leishmaniasis (CL); Buruli ulcer (BU); deep mycoses, including mycetoma, sporotrichosis and others; scabies; yaws (better known as "bouba" in Angola); and snakebites and envenoming.

This is a retrospective analysis of the documents and records collected from 2017 to 2021 by the National directorate of public health (DNSP), complemented by data on skin-NTDs from field investigations, geographical mapping, and other sources of information, including WHO reports.

Results

The 2017-2021 administratively reported cases of skin-NTDs are presented in [table 1](#)^{2,3}. Most were diagnosed on a clinical basis. Laboratory examinations such as microscopy of blood smears and of skin preparations stained with Giemsa, Ziehl-Neelsen procedure and/or other special colorations, cultures, and histopathological analyses of biopsy material were performed in a minority of cases, as functional laboratory facilities and histopathology services are inadequate outside of the most populated provinces, such as Luanda, Huila, and Huambo.

Polymerase chain reaction (PCR) tests performed in reported and published cases of LF, BU, and CL were all carried out in foreign recognized laboratories. Rapid immunological screening tests to detect yaws (SD Bioline Syphilis 3.0 and dual path platform Syphilis Screen and Confirm assay) were used to test clinically suspected cases. The Alere™ Filariasis test strip (FTS) was used in LF mapping surveys and to monitor the qualitative detection of *Wuchereria bancrofti*³.

Leprosy (Hansen's disease)

In 2005, the prevalence rate of leprosy level passed below the level of one case per 10,000, reaching the goal of "leprosy elimination as a public health problem", as defined by the WHO⁴. As shown in [figure 1A](#), the number of newly detected cases decreased from 4272 in 2002 to 431 in 2012, with yet a high proportion of new cases in children under 15 years (12.8%), and

Table 1. Reported cases of skin-related neglected tropical diseases 2017-2021, National Directorate of Public Health

S-NTDs	2017	2018	2019	2020	2021	Endemic areas
Leprosy						All 18 provinces (2021)
– Newly detected cases	605	847	721	422	797	
– Rate/million pop	20.31	27.49	22.66	12.84	23.90	
– Cases under treatment	1018	1070	1070	1870	1785	
– Prevalence rate/million population	34.18	37.73	33.62	56.90	53.00	
– New child cases	35	68	116	56	93	
(% of new cases)	(5.8)	(8.0)	(16.1)	(13.3)	(11.7)	
– New cases with G2D	98	145	112	20	187	
(% of new cases)	(16.2)	(17.1)	(15.5)	(4.7)	(23.5)	
– Multi-bacillary new cases	578	795	637	361	681	
(% of new cases)	(95.5)	(93.9)	(88.3)	(85.5)	(85.4)	
Onchocerciasis						
– New cases	603	238	288	838	1110	48 municipalities (29.3%) in 10 provinces (2021)
Lymphatic filariasis						
– New cases of lymphedema/hydrocele	No data	No data	No data	No data	No data	38 municipalities (23.2%) in 12 provinces (2021)
Guinea worm (dracunculiasis)						
– New cases	0	1	1	1	0	3 municipalities in Cunene province (2018-2020)
Cutaneous leishmaniasis						
– PCR confirmed cases	2	0	0	0	0	Londumbali municipality in Huambo province (2017)
– Suspected cases	53	19	0	0	0	
Buruli ulcer						
– PCR confirmed cases	0	0	0	0	3	Mbanza Congo municipality in Zaire province (2021)
Deep mycoses						
– New cases	No data	No data	No data	No data	No data	Sporadic cases countrywide
Scabies						
– Cases	13,2747	52,983	54,996	15,738	No data	Countrywide
Yaws						
– Cases	0	0	0	0	0	Unknown current status
Snakebites						
– Cases	No data	No data	No data	522	581	Countrywide, data from 14 provinces
– Deaths	No data	No data	No data	35	41	

multi-bacillary cases (MB) (69.3%), suggestive of continuous disease transmission in affected communities⁵. From 2012 onward, the number of newly annually reported cases increased again progressively to 605 in 2017⁶ and to 797 in 2021⁷, accompanied by a concomitant increase in the proportion of new pediatric, G2D and MB cases (Table 1); 75% of all cases were males and 25% were females⁸; the disease was endemic in all provinces, with 82% of all reported new cases congregated in nine provinces, including Luanda⁸ (Fig. 1B).

Filariasis

Notification of onchocerciasis is mandatory but most reported cases are not confirmed by microscopy of skin snip biopsies. The first mapping of onchocerciasis was

performed in 2002 using the rapid epidemiological mapping for onchocerciasis (REMO) method assessing the number and percentage of villages with people presenting *Onchocerca* skin nodules in a given area^{9,10}. In 2015, the REMO assessment was complemented by surveys using skin snip biopsies. In 2021, the WHO reported 48 municipalities (29%) as endemic, distributed in 10 provinces, with the highest prevalence rates in Bie, Huambo, and Cuando Cubango^{3,11} (Fig. 2A). The status of the remaining 116 municipalities is unknown and requires further investigations.

LF scrotal hydrocele and limb lymphedema are not subject to mandatory notification. National mapping of LF was carried out from 2015 to 2017 in three phases, using the FTS (Alere™). The 2021 WHO data showed LF endemicity in 38 municipalities (23.2%) distributed

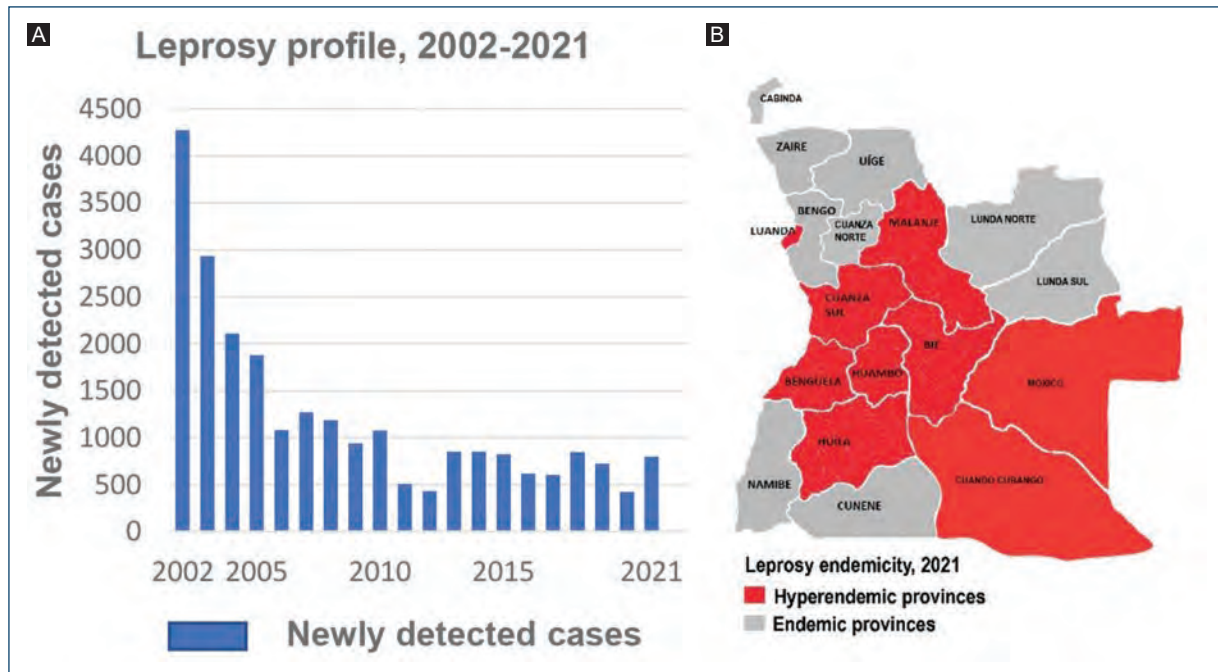


Figure 1. Leprosy in Angola. **A:** profile of newly detected cases, 2002-2021. **B:** provinces with 82% of all reported new cases in 2021.

in 12 provinces (Fig. 2B), and a disease prevalence ranging from 1% to 12%. Onchocerciasis and LF were coendemic in 15 municipalities and 7 provinces^{3,11}. In 2020, the WHO estimated the total population requiring mass administration of ivermectin and albendazole (IA) to be 3,819,439; and 33 of the 38 LF endemic municipalities had started to implement IA mass drug administration (MDA) programs¹².

The prevalence of *Onchocerca volvulus*, *W. bancrofti*, and *Loa Loa* infections was also assessed in Bengo province in 2017 and 2020 with a combination of clinical, serological, and DNA diagnostics^{13,14}. Overall, low levels of endemicity with variable overlapping distributions were observed in 22 communities. Onchocerciasis prevalence was 5.3% in eight communities and LF-related lymphedema and/or hydrocoele were found in 27 individuals (1.7%).

GWD or Dracunculiasis

Angola, not known for GW cases, reported from 2018 to 2020 three PCR confirmed cases of human GWD infection¹⁵. All cases were found in three chronically drought affected municipalities of Cunene province, bordering Angola with Namibia¹⁶ (Fig. 3A). The first case (Fig. 3B) was detected in 2018 through a

nationwide GWD case search carried out during a national immunization campaign against measles and rubella¹⁷.

Alongside the reported cases of human infections, the detection in 2022 in the same province of eight cases of GWD infections in dogs (Fig. 3C) was a finding of particular importance³.

Cutaneous leishmaniasis

The first confirmed cases of CL in Angola were reported in 1969 by Bréchet at the Caluquembe missionary Hospital, in two patients hailing, respectively, from Huila and Cuanza Sul provinces¹⁸ (Fig. 4A). The patient from Cuanza Sul presented with multiple infiltrated lesions, nodules, and some ulcers, which were initially misdiagnosed and treated as atypical lepromatous leprosy, until the correct diagnosis of CL was clearly established by histopathological examination of the ear lesion (Fig. 4B).

In 1994, Jimenez et al.¹⁹ published the case of a 26-year-old man with no history of travel outside Angola who consulted and presented in Spain with typical symptoms of visceral leishmaniasis. The parasite was isolated and biochemically characterized as *Leishmania infantum*. According to Jimenez et al., this

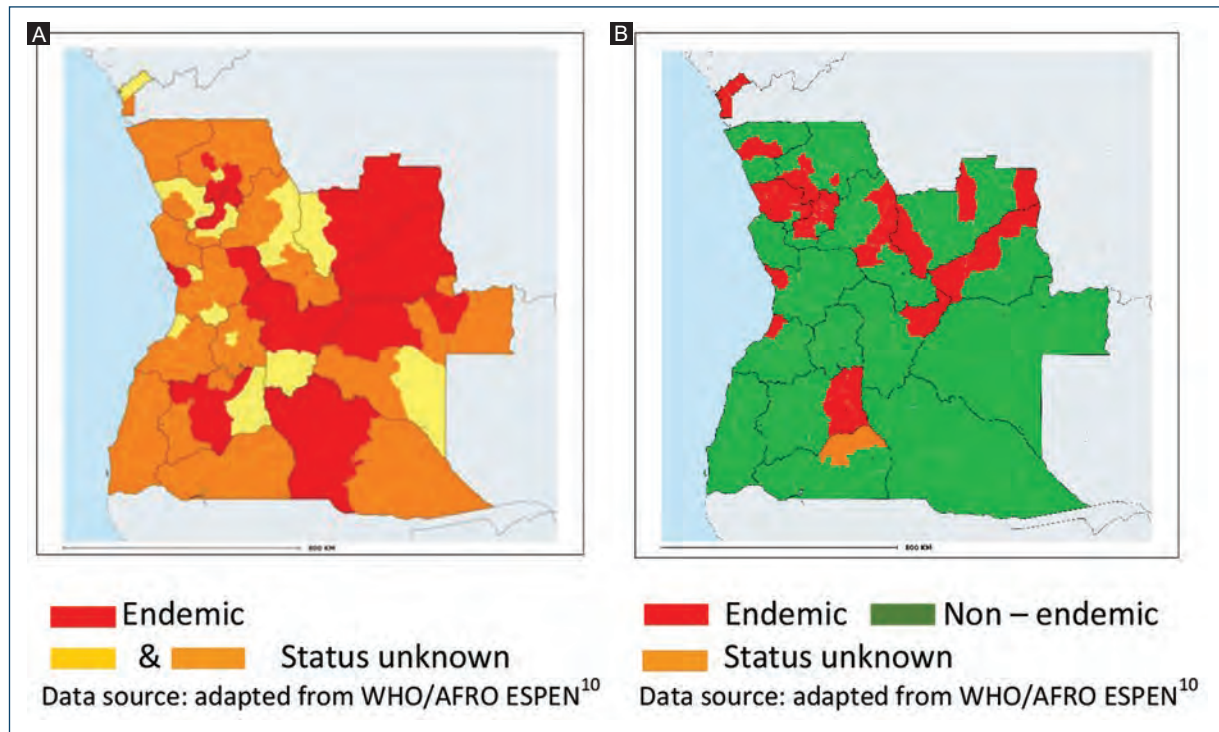


Figure 2. Mapping of filariasis endemicity, 2021. **A:** onchocerciasis. **B:** lymphatic filariasis.

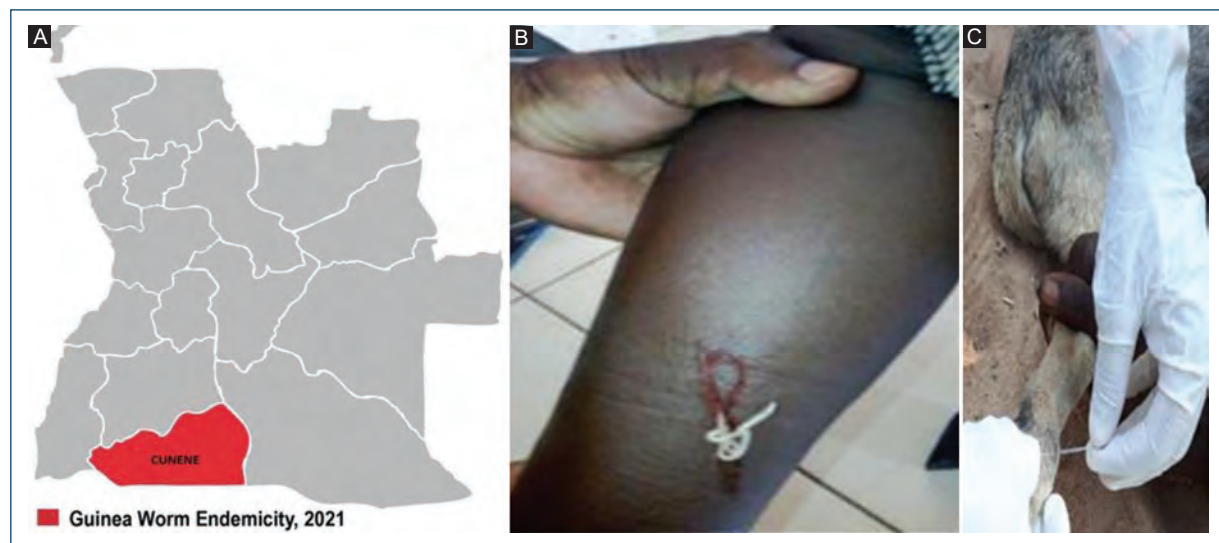


Figure 3. Guinea worm. **A:** cunene province, bordering Angola with Namibia. **B:** human GWD. **C:** canine GWD (back leg).

was the first report of *L. infantum* identified in Africa, south of the equator.

Between 2017 and 2019, 71 clinically suspected cases of CL were identified through active community case detection in the municipality of Londuimbali in Huambo

province²⁰. Most of the lesions observed (88.7%) in those cases were round or oval painless ulcers located in exposed areas (Fig. 4C), showing a reddish and firm base, often covered with crusts, with elevated and well-defined borders. Material from three biopsies was sent for



Figure 4. Cutaneous leishmaniasis. **A:** provinces of Cuanza-Sul, Huíla, and Huambo. **B:** case from Cuanza Sul showing multiple ear infiltrations and nodules. **C:** ulcer in a case from Londuimbali, Huambo province.



Figure 5. Buruli ulcer endemicity, 1998-2021. **A:** Bengo, Uíge, Malange, and Zaire provinces where cases have been reported. **B** and **C:** cases from Zaire province, 2021.

molecular analysis to the Lisbon Institute of Hygiene and Tropical Medicine; two of the samples, from patients aged 18 and 26 years, were reported as PCR positive for *Leishmania* spp. DNA²¹. Laboratory investigations were not carried out in other clinically suspected cases.

Dogs are known as a main reservoir for human infection. In 2014, a serological and molecular survey of *Leishmania* infection was carried out in 103 dogs in the capital city of Luanda, by Vilhena et al.²². One autochthonous dog was found PCR positive for *L. infantum*, Canine leishmaniosis (CanL).

Buruli ulcer

In 1998, Bär et al.²³ published the first reported Angolan case of BU, a 2.5-year-old boy from Bengo

province (Fig. 5A) referred to Germany for diagnosis and treatment of severe malnutrition (Kwashiorkor) and of a large thoracic chronic ulcer. *Mycobacterium ulcerans* was identified from the ulcer by histological examination, PCR, and culture.

In 2003, 27 cases were reported among Angolan refugees²⁴, diagnosed and treated at the Kimpese Hospital, Bas-Congo region, DR Congo. In 2018, a joint Angolan MOH/WHO team went on a fact-finding mission and reported the presence in the same institution of nine patients with BU, hailing from the northern provinces of Angola²⁵ (Fig. 5A). Following the resolution of the internal conflict in 2002, the cross-border movement of goods and people between Angola and the DR Congo, still highly endemic to BU²⁶, returned to a complete normalization.



Figure 6. Scabies. **A:** scabies with secondary skin infection in a child from Huila province. **B** and **C:** crusted (Norwegian) scabies in an HIV/AIDS patient successfully treated with ivermectin and permethrin.

In 2018, another report²⁶ described two laboratory-confirmed cases, most likely acquired in Kafufu/Luremo villages located in the Malange province (Fig. 5A), along the Cuango river bordering North and East Angola with the DR Congo. These patients were living close to potentially contaminated aquatic environments, where artisanal alluvial mining activities are widespread, a factor considered as a risk factor for acquiring BU^{26,27}.

In 2021, a MOH/WHO team, including a dermatologist, carried out a cross-border investigation in three border municipalities of Zaire and Uíge provinces, to actively search for cases of BU, leprosy, yaws, GWD, and African Human Trypanosomiasis. The mission detected a high number of common dermatoses, a case of leprosy and three autochthonous new BU cases in Mbanza Congo municipality, Zaire province (Fig 5A-C), all confirmed by PCR²⁸. Angola was recognized in 2021 by the WHO as a new endemic country for BU.

Deep fungal infections

The epidemiology of these infections is poorly known due to weak laboratory services and lack of mandatory notification. Sporadic cases of mycetoma, chromoblasto-mycosis, sporotrichosis, and African histoplasmosis – occasionally associated with HIV/AIDS (Fig. 7B) – occur countrywide and often end up referred at an advanced stage for diagnosis and treatment to provincial hospitals and/or dermatology services²⁹.

Scabies

Scabies is widespread in Angola (Table 1) but largely underreported and its real burden and distribution is largely unknown. Subnational data show many cases and frequent outbreaks reported in southern provinces, in areas particularly affected by drought and poverty. Scabies is the most common skin NTD diagnosed in dermatology outpatient services²⁹, often associated with bacterial infection (Fig. 6A) and, in crusted scabies cases, with HIV/AIDS (Fig. 6B and C).

Yaws/Bouba

Angola is among the countries known to have been endemic for yaws in the 1950s, but its current status is unknown³⁰. In 2021, an integrated skin NTD survey, including a search for yaws, was carried out in the northern provinces of Zaire and Uíge, combining clinical examination and the use of rapid screening tests in 76 suspected cases. None tested positive for yaws²⁷.

Snakebite envenoming

In 2020 and 2021, a total of 14 provinces reported, respectively, 522 and 581 cases of snakebites with 35 and 41 deaths (6.7%/7.1%) (Table 1). Most cases were notified in northern and central provinces, namely, Uíge, Cabinda, Cuanza Norte, Cuanza Sul, and Benguela. No single case was notified in the capital city of Luanda. Under-reporting of snake bite incidence and mortality is common.



Figure 7. **A:** histoid leprosy. **B:** african histoplasmosis in a patient with HIV/AIDS. **C:** dermatologist involved in community information, education and mobilization activities.

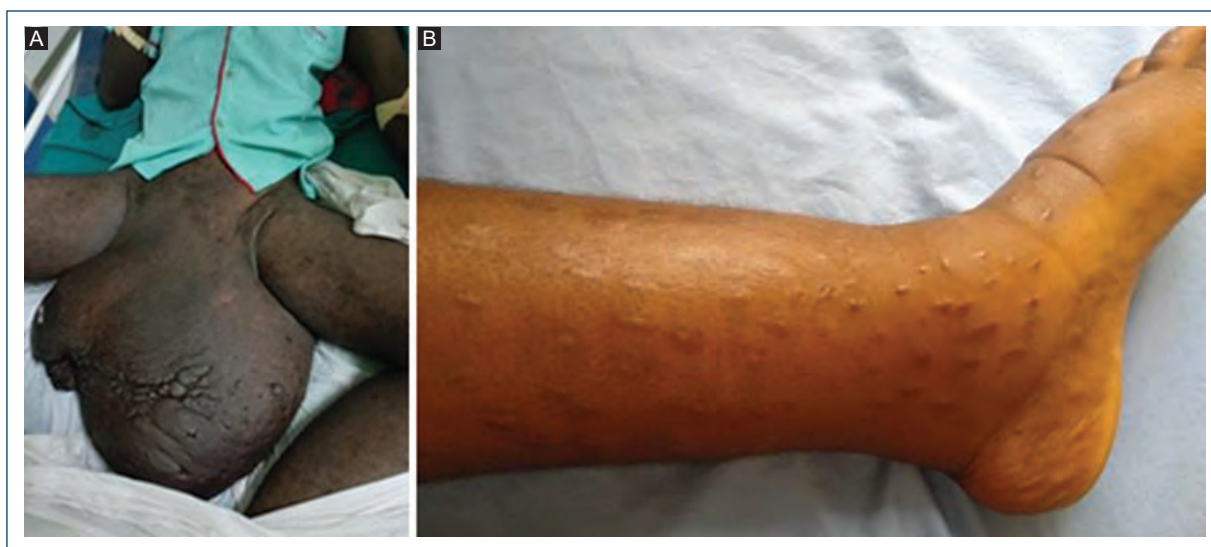


Figure 8. **A:** LF scrotal hydrocele. **B:** filariasis lymphoedema with scarification scars.

Discussion

Poor community knowledge on skin NTDs, late or missed diagnoses by health workers and limited access to laboratory confirmation of suspected cases are key challenges to overcome. At a time of renewed national and international efforts to control and eliminate skin-NTDs^{1,3}, there is a dire need to improve knowledge on their burden and geographical distribution, by improving integrated surveillance, field surveys, and clinical investigations.

Dermatologists are key actors in fighting the neglect affecting skin-NTDs, offering expertise in the differential diagnosis of skin lesions such as discolored patches, nodules, and ulcers, facilitating the access to specific laboratory examinations, and helping in managing rare and/or difficult cases (Fig. 7A and B).

Since 2002, a growing number of national dermatologists have been trained locally and abroad, reaching a total of 37 in 2021, distributed in six provinces³¹. Some are already engaged in contact tracing, integrated clinical

surveys, and diseases monitoring as well as capacity building and community mobilization activities (Fig. 7C).

Strengthened laboratory services including SOPs, direct microscopy, improved access to rapid tests, and PCRs are essential to confirm suspected cases, as the clinical diagnosis of skin-NTDs can be challenging, particularly for early-stage lesions^{1,32}.

The collection of quality data on skin-NTDs, on which programmatic decisions should be based, is a well-recognized challenge. For a number of reasons, most data set are incomplete and fragmented. Mandatory notifications, required currently only for leprosy and onchocerciasis, should include ideally all skin-NTDs. According to the national epidemiologic bulletin³³, only 79.6% of the expected provincial reports were received at the central level (DNSP) in 2021. Most data entries and analysis at the periphery are still paper-based, leaving ample room for mistakes and omissions.

The recommended WHO digital data platform “district health information system version 2”¹ is being tested for leprosy, but not yet in routine use³. Its accelerated introduction should be given special attention to improve qualitatively and quantitatively the registration and monitoring of skin NTDs and to streamline the use of data for integrated program planning and implementation.

Disease mapping is a powerful tool to understand and monitor the geographic distribution of skin-NTDs, helping to orient integrated program planning, training of health workers, field investigations, treatment strategies, and drug's logistic, including anti-venom sera. Our data show significant geographic variations of skin-NTDs endemicity, ranging from a single province for GWD (Fig. 3A), to all provinces for leprosy (Fig. 1B). Multiple skin-NTDs are coendemic in many communities, municipalities, and provinces.

As observed in other countries⁶, the COVID-19 pandemic negatively affected the functioning of health services and public health programs, leading in 2020 to a reduction in the number of newly detected and reported skin-NTD cases (Table 1).

Skin-related NTDs, and leprosy in particular, have historically been studied and managed in Angola by leprologists and public health specialists through scientific missions. The “vertical” control program with leprosaria and mobile teams, established in 1958, was integrated in 2002 in the primary health-care system³⁴ with positive results (Fig. 1A). Leprosy services were however later negatively impacted by dwindling clinical and program management expertise as well as funding, a trend favorably compensated by the expanding number of trained dermatologists³¹.

The persisting low-grade transmission of leprosy following its “elimination as a public health problem” calls meanwhile for further epidemiological and clinical investigations to detect where and why the elimination process is not moving forward. The relatively high proportion of G2D in newly detected cases reflects a delay in disease detection, resulting from low community awareness, delay in seeking care, weak active case finding and contact tracing, and/or limited capacity of the health system to early recognize leprosy⁶. Furthermore, in 2021, Angola's rates of new cases detection (23.09/million population), disease prevalence (53.00/million), new cases in children below 15 years (5.96/million), and new cases with G2D (5.41/million) were much higher than the respective rates for the African Region (18.01/million: 24.3/million; 4.34/million; 2.78/million)⁷.

Angola is considered by the WHO as a priority country for onchocerciasis and LF control and elimination¹², but available data and studies are scarce and limited to monitor the burden of those diseases. LF is an avoidable, debilitating, disfiguring vector-borne disease, caused by *W. bancrofti* infection. Most infections occur during childhood and are initially asymptomatic. Scrotal hydrocele and limb's elephantiasis (Fig. 8A and B) are the visible clinical consequences of the chronic lymphatic vessel damage. Late diagnosis and treatment of these conditions are common. As an example, the 16-year-old girl shown in (Fig. 6B) presented early signs of lymphedema at the age of 12, and was treated for various conditions, including with traditional skin scarification, until a dermatologist made 4 years later the correct – laboratory confirmed – diagnosis of LF infection.

GWD, a crippling parasitic disease today on the verge of global eradication, was highly endemic in 20 countries in the mid-1980s. As a result of extensive and sustained control and elimination activities, only 15 cases were globally reported in 2021, including eight cases from Chad, one from Ethiopia, two from Mali, and four from South Sudan³⁵.

While Angola was declared by the WHO in 2020 as a newly endemic country for GWD, neighboring Namibia has never been endemic and has been certified free of the disease in 1999¹⁵. The two countries have set a good example of active cross-border collaboration for GWD case detection, surveillance, and follow-up¹⁵⁻¹⁷.

The detection in 2022 in Cunene province of eight cases of GWD infections in dogs, despite the implementation of all classical public health control and elimination strategies, set a particular challenge regarding



Figure 9. Snakebites. **A:** *bitis gabonica* as cover picture of “Snakes in Angola” from Paula Oliveira. **B:** status after extensive surgical debridement of necrotic tissue, compatible with snakebite of *Bitis* or *Naja* species.

the elimination of the disease in humans. A similar situation has been observed in Chad and Mali, where enhanced access to safe drinking water, education, surveillance, case containment, vector control, and monetary incentives for reporting cases have failed so far to prevent the circulation of *Dracunculus Medinensis* in dogs³⁵.

While visceral and CL are endemic in North, West, and East Africa, very little is known about the transmission of the disease in Angola and other Southern African countries³⁶. Canine leishmaniosis, a global zoonosis acting as a reservoir for human infections, is endemic in more than 70 countries in Europe, North Africa, Asia, and America, but information on its status in Southern Africa is very limited²². Further epidemiological and clinical investigations are required to better define the burden and distribution of CL in Angola.

First described in Australia in 1948, BU is an infection of particular importance in West and Central Africa^{25,37}. BU is caused by *M. ulcerans*, an environmental bacterium producing the mycolactone toxin causing extensive tissue damage and inhibition of the immune response. The exact mode of transmission of *M. ulcerans* remains uncertain. BU starts clinically with a papule, nodule, plaque, or edematous lesion that eventually progress to a chronic indolent necrotizing disease of the skin, subcutaneous tissue, and sometimes bone. Atypical forms can be confounded with other causes of skin ulcers and PCR testing is thus required to confirm the clinical diagnosis³².

Yaws, or bouba as known locally, is a non-venereal treponemal infection affecting mostly children under

15 years of age, caused by *Treponema pallidum* ssp. *pertenue*, leading to skin, bone, and cartilage lesions. Despite its currently unknown status, yaws should not be forgotten as its endemicity persists in the neighboring DR Congo and in the Congo Republic. Further investigations, especially in border municipalities, are required to detect its eventual presence in Angola especially in poor communities living at the “end of the road,” far from health services³⁰.

Although Scabies and other ectoparasitosis have been added in 2017 by the WHO to the list of skin-related NTDs, these common diseases are not yet formally integrated into the national NTD control program. Formal assessments of the local burden of scabies will allow to better identify the areas which would benefit of Ivermectin MDA. While the management of scabies is relatively simple and inexpensive, the access to quality medications is limited in many peri-urban and rural areas. A potential impact on scabies of Ivermectin currently given in mass drug administration (MDA) programs to control filariasis in endemic municipalities^{3,12} would deserve further studies.

Snakebites incidence in Angola is unknown, but probably high if we consider available data from DR Congo, where between 120 and 450 bites/100,000 inhabitants/year are recorded³⁸. According to Ceriaco and Marques³⁹, more than 120 species of snakes have been identified so far in Angola, including 34 potentially harmful to humans. The big vipers belonging to the *Bitis* species (Fig. 9A), spitting *Naja nigricollis*, and Mamba (*Dendroaspis*) species are reported as those biting most frequently, causing often severe skin lesions or fatal envenomation³⁸. Beside systemic manifestations, local pain and lesions such as swelling, blisters, bleeding, and tissue necrosis are common (Fig. 9B). Dermatologists tend to see few snakebites as many cases either do not reach health facilities, or are referred directly to emergency surgery or medicine services.

Conclusion

Except for yaws – whose status is presently unknown but which should not be forgotten – all skin NTDs included in our review remain endemic locally or countrywide. As observed for leprosy, BU, CL, and GWD, elimination of those diseases as a public health problem does not warrant total interruption of transmission with time.

Epidemiological searches carried out in recent years have revealed unknown foci of BU, CL, and GWD.

The search and detection in dogs of GWD and leishmaniasis are of critical importance, given their known implications as reservoir for the transmission of those diseases to humans.

Leprosy remains endemic in all provinces with, since 2012, a stagnant elimination process requiring special attention. Interest and investment in operational research are essential.

The incorporation of CL, yaws, deep fungal infections, scabies, snakebites, and envenoming in the national NTD master's plans should lead to a better assessment of the burden and distribution of those diseases and improve case management.

As stakeholders of the coalition working for the control and elimination of skin NTDs, Angolan dermatologists save wasted resources caused by missed and late diagnosis of skin NTDs. They are called on to support more actively integrated approaches related to advocacy, disease surveillance, field investigations, and capacity building activities^{40,41}.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. World Health Organization. Ending the Neglect to Attain the Sustainable Development Goals: A Road Map for Neglected Tropical Diseases 2021-2030. Geneva: World Health Organization; 2020. Available from: <https://apps.who.int/iris/handle/10665/338565>
2. Ministério da Saúde. Plano Estratégico Nacional de Doenças Tropicais Negligenciadas 2017-2021. Luanda, Angola: DNSP/Ministério da Saúde; 2017.
3. Ministério da Saúde. Plano Estratégico Nacional de Doenças Tropicais Negligenciadas 2021-2025. Luanda, Angola: DNSP/Ministério da Saúde; 2022.
4. WHO. Global leprosy situation, 2005. Wkly Epidemiol Rec. 2005;80:289-95.
5. World Health Organization. Global leprosy: update on the 2012 situation. Wkly Epidemiol Rec. 2013;35:365-79.
6. WHO. Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control. Wkly Epidemiol Rec. 2021;96:421-44.
7. WHO. Global leprosy (Hansen disease) update, 2021: moving towards interruption of transmission. Wkly Epidemiol Rec. 2022;97:429-50.
8. Afonso E. Reconhecimento das Doenças Tropicais Negligenciadas através das alterações da pele e a situação da lepra em Angola. In Comunicação nas Jornadas de Dermatologia do Hospital Américo Boavida, Luanda, Angola, 2022.
9. WHO. African Programme for Onchocerciasis Control, Nwoke BE, Eyongo P, Namssenmo A, Kankou JM, et al. Rapid Epidemiological Mapping of Onchocerciasis (REMO) in Angola, Jan. 25-Feb. 28, 2002: Mission Report. African Programme for Onchocerciasis Control (APOC). Available from: <https://apps.who.int/iris/handle/10665/348713>
10. WHO/African Programme for Onchocerciasis Control, António JP. Completion of Rapid Epidemiological Mapping of Onchocerciasis (REMO) in Angola, 14 January to 8 February 2003. Survey Report for WHO/African Programme for Onchocerciasis Control (APOC). Available from: <https://apps.who.int/iris/handle/10665/348713>
11. WHO/AFRO Expanded Special Project for the Elimination of Neglected Tropical Diseases. Available from: www.espen.afro.who.int
12. WHO. Global programme to eliminate lymphatic filariasis: progress report, 2020. Wkly Epidemiol Rec. 2021;41:497-508.
13. Brito M, Paulo R, Van-Dúnem P, Martins A, Unnasche TR, Novake RJ, et al. Rapid integrated clinical survey to determine prevalence and co-distribution patterns of lymphatic filariasis and onchocerciasis in a *Loa loa* co-endemic area: The Angolan experience. Parasite Epidemiol Control. 2017;2:71-84.
14. Paulo R, Brito M, Van-Dúnem P, Martins A, Novak RJ, Jacob B, et al. Clinical, serological and DNA testing in Bengo province, Angola further reveals low filarial endemicity and opportunities for disease elimination. Parasite Epidemiol Control. 2020;11:e00183.
15. WHO. Disease Surveillance Confirms Presence of Dracunculiasis in Angola. Geneva: World Health Organization; 2018. Available from: <https://www.disease-surveillance-confirms-presence-of-dracunculiasis-in-angola-who.int>
16. WHO Regional Office for Africa. Strengthening Surveillance for Guinea Worm Disease in Northern Namibia; 2019. Available from: <https://www.strengthening-surveillance-for-guinea-worm-disease-in-northern-namibia-whoregional-office-for-africa>
17. WHO Regional Office for Africa. Namibia and Angola Strengthen Cross-border Collaboration for Disease Prevention and Control; 2022. Available from: <https://www.namibia-and-angola-strengthen-cross-border-collaboration-for-disease-prevention-and-control-who-regional-office-for-africa>
18. Brechet RA, Rivers-Kirby J. Dois casos de Leishmaniose cutânea em Angola. Rev Méd Angola. 1969;45:17-22.
19. Jimenez M, Puente S, Gutierrez-Solar B, Martinez P, Alvar J. Visceral leishmaniasis in Angola due to *Leishmania (Leishmania) infantum*. Am J Trop Med Hyg. 1994;50:687-92.
20. Pedro JM. Cutaneous leishmaniasis in Angola: an historical report of a continued focus of transmission in Huambo province. In Communication at the 2022 Jornadas de Dermatologia do Hospital Américo Boavida, Luanda, Angola, 2022.
21. Cortes S, Pereira A, Vasconcelos J, Paixão JP, Quivinja J, De Moraes Afonso J, et al. Leishmaniasis in Angola-an emerging disease? BMJ Glob Health. 2019;4:A1-68, A47.
22. Vilhena H, Granada S, Oliveira AC, Schallig HD, Nachum-Biala Y, Cardoso L, et al. Serological and molecular survey of *Leishmania* infection in dogs from Luanda, Angola. Parasit Vectors. 2014;7:114.
23. Bär W, Rüscher-Gerdes S, Richter E, de Bär GM, Dittmer C, Papsdorf H, et al. *Mycobacterium ulcerans* infection in a child from Angola: diagnosis by direct detection and culture. Trop Med Int Health. 1998;3:189-96.
24. Kibadi K, Tsakala M, Moutu-Yamba JB, Muyembe T, Kashongwe M, Imposso B, et al. L'ulcère de Buruli chez les réfugiés angolais des sites de Kimpese, Bas-Congo, RD Congo. Sante. 2003;13:39-41.
25. Afonso E, Caquece FH, Ndembe Y. Relatório Sobre a Visita ao Hospital de Kimpese, Província do Congo Central, RDC, Para Úlcera de Buruli. Luanda: DNSP/MINSA; 2018.

26. Kibadi K, Panda M, Tamfum JJ, Fraga AG, Filho AL, Anyo G, et al. New foci of Buruli ulcer, Angola and democratic republic of Congo. *Emerg Infect Dis*. 2018;11:1790-92.
27. Van der Werf TS, Stienstra Y, Johnson RC, Phillips R, Adjei O, Fleischer B, et al. *Mycobacterium ulcerans* disease. *Bull World Health Organ*. 2005;83:784-91.
28. MINSA/WHO. Projecto de Redução do Fardo da Lepra em Angola: Relatório de Avaliação Transfronteiriça Angola/RDC. Luanda: Ministério da Saúde; 2021.
29. Baptista M, Garcia C, Alberto P, Isaías J. Casuística da Consulta Externa de Dermatologia do Hospital Américo Boavida (HAB), Janeiro-Outubro 2019. In: Comunicação No 3 Workshop de Dermatologia do HAB, Luanda; 2019.
30. World Health Organization. Eradication of yaws - the Morges strategy. *Wkly Epidemiol Rec*. 2012;20(87):189-94.
31. De Almeida Voumard L. Projecto Angolano de formação e desenvolvimento da dermatologia: avanços e desafios. *J Port Soc Dermatol Vene-reol*. 2018;76:261-8.
32. Toutous-Trellu L, Nkemenang P, Comte E, Ehounou G, Atangana P, Mboua DJ, et al. Differential diagnosis of skin ulcers in a *Mycobacterium ulcerans* endemic area: data from a prospective study in Cameroon. *PLoS Negl Trop Dis*. 2016;10:e0004385.
33. Direcção Nacional de Saúde Pública, Ministério da Saúde. Boletim Epidemiológico. 21th ed. Brasil: Ministério da Saúde; 2021.
34. De Almeida Voumard L. A dermatologia em Angola: evolução e desafios. *Med Cutan Iber Lat Am*. 2021;49:77-85.
35. WHO. Dracunculiasis eradication: global surveillance summary, 2021. *Wkly Epidemiol Rec*. 2022;21/22,97:225-48.
36. WHO. Global leishmaniasis surveillance 2019-2020, a baseline for the 2030 roadmap. *Wkly Epidemiol Rec*. 2021;35:401-19.
37. Yotsu RR, Suzuki K, Simmonds RE, Bedimo R, Ablordey A, Yeboah-Manu D, et al. Buruli ulcer: a review of the current knowledge. *Curr Trop Med Rep*. 2018;5:247-56.
38. De Oliveira PR. Serpentes em Angola, Uma Visão toxicológica e Clínica Dos Envenenamentos. Edição Glaciár. Lisboa, Portugal; 2017.
39. Ceriaco LM, Marques MP. Serpentes Venenosas de Angola. Guia de Identificação e Primeiros Socorros. Edição Arte e Ciência. Lisboa, Portugal; 2021.
40. Engelman D, Fuller LC, Solomon AW, McCarthy JS, Hay RJ, Lammie PJ, et al. Opportunities for integrated control of neglected tropical diseases that affect the skin. *Trends Parasitol*. 2016;32:843-54.
41. World Health Organization. Ending the Neglect to Attain the Sustainable Development Goals: A Strategic Framework for Integrated Control and Management of Skin-related Neglected Tropical Diseases. Geneva: World Health Organization; 2022. Available from: <https://www.who.int/publications/i/item/9789240051423>

The clinicopathological manifestations and differential diagnoses of mycosis fungoides variants (the great mimickers): a comprehensive review

As manifestações clinicopatológicas e diagnósticos diferenciais de variantes de micose fungoides (os grandes imitadores): uma revisão abrangente

Jacob Al-Dabbagh^{1,2,a*}, Nemat Ismail^{1,b}, Moath Alsoleman³, Eman Mohammad-Deeb¹, Lina Al-Soufi^{1,c}, and Zuheir Al-Shehaby^{2,d}

¹Faculty of Medicine, Tishreen University, Latakia; ²Cancer Research Center, Tishreen University, Latakia; ³Faculty of Medicine, Damascus University, Damascus, Syria

ORCID: ^a0000-0002-5596-9738; ^b0000-0002-0206-1080; ^c0000-0003-4351-7344; ^d0000-0002-6519-7954

Abstract

Mycosis fungoides (MF) is the most prevalent type of primary cutaneous T-cell lymphoma (CTCL), which is considered a great imitator due to the wide spectrum of its clinical manifestations that can mimic numerous skin disorders. MF can also resemble a wide range of dermatoses on histopathological and clinicopathological bases. The various clinical and histopathological manifestations of MF often lead to missing or delaying the diagnosis, which leads to a poorer prognosis as a consequence. In this article, we presented a comprehensive review of the clinical presentations and differential diagnoses of the clinical, histopathological, and clinicopathological variants of MF with a focus on the histopathologic manifestations of each variant.

Keywords: Cutaneous lymphoma. Cutaneous T-cell lymphoma. Mycosis fungoides. Mycosis fungoides variants. Skin cancer.

Resumo

A micose fungóide (MF) é o tipo mais prevalente de linfoma cutâneo primário de células T, que é considerado um grande imitador devido ao vasto espectro das suas manifestações clínicas e ainda porque a MF pode assemelhar-se a uma vasta gama de dermatoses com idênticas bases histopatológicas e clinicopatológicas. As várias manifestações clínicas e histopatológicas de MF conduzem frequentemente a uma falta ou atraso no diagnóstico, o que leva a um prognóstico mais pobre. Neste artigo, apresentámos uma revisão abrangente das apresentações clínicas e diagnósticos diferenciais das variantes clínicas, histopatológicas e clinicopatológicas de MF com enfoque nas manifestações histopatológicas de cada variante.

Palavras-chave: Linfoma cutâneo. Linfoma cutâneo de células T. Micose fungóide. Variantes de micose fungóide. Cancro da pele.

*Correspondence:

Jacob Al-Dabbagh
E-mail: jacobaldabbagh0@gmail.com

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Introduction

Mycosis fungoides (MF) is the most common type of CTCL, which represents about 50% of all primary cutaneous lymphomas^{1,2}. It was first described by Jean Alibert in 1806².

MF affects mainly adults, mostly males². Black populations have a higher rate of MF and worse prognosis³.

Atypical cerebriform lymphocytes in the epidermis and superficial dermis are the main histopathologic feature of MF^{4,5}, but, as some skin disorders have similar histopathological features, this may lead to misdiagnosis⁶. Therefore, the diagnosis of MF is a real challenge to physicians and needs an association between clinical and histopathological examinations, as many skin disorders may mimic the various variants of MF^{1,6,7}.

This article provides a comprehensive review of MF variants with a focus on their differential diagnoses and distinct characteristics to approach the most likely diagnosis of each variant.

Classification and variants

Aside from classic MF, many clinical, histopathologic, and clinicopathologic variants of MF have been reported (Table 1)^{4,8}. Since the majority of variants exhibit a clinical behavior comparable to that of classic MF, they are not classified separately in recent classifications¹. Only folliculotropic MF (FMF), pagetoid reticulosis (PR), and granulomatous slack skin (GSS) are recognized as distinct variants of MF in the World health organization: European Organization of Research and Treatment of Cancer (WHO-EORTC) classification due to their distinct clinicopathologic features, clinical behavior, and/or prognosis¹.

Classic MF

Classic MF, also known as Alibert–Bazin type of MF, is the most reported type of this CTCL^{1,2,6}. It represents about 90% of all MF cases and accounts for approximately 4% of all non-Hodgkin lymphomas^{2,6}.

Males are more frequently affected⁹, typically adults in their 5th–6th decade⁹.

It is classified into three stages that include patch, plaque, and tumor stages⁶. Asymmetric telangiectasias and erythematous macules are the clinical manifestations of patch-stage MF⁶, which typically involves sun-protected areas like the breast (in female patients),

buttocks, and trunk and extremities⁶. The plaque stage is usually characterized by erythematous, reddish-brown, or scaling lesions⁶. The last stage is characterized by nodules ≥ 1 cm⁶.

The stage of classic MF determines its prognosis⁹. Early-stage patients have an excellent prognosis and a survival rate comparable to that of age, sex, and race-matched individuals⁹, whereas advanced-stage patients over 60 years old are considered with a poor prognosis⁹. Anyway, most MF patients have a slow clinical progression over years or decades⁹.

The histopathological hallmark in the patch stage is the proliferation of large pleomorphic lymphocytes at the dermal-epidermal junction, focal parakeratosis, and papillary dermis fibrosis⁶. The plaque stage highly resembles the patch stage and reveals inter-surface vascular changes like infiltration of the upper dermis by lymphocytes, which characteristically have hyperchromatic nuclei and nuclear membranes which are convoluted, in addition to Pautrier's microabscesses⁶. Neoplastic lymphocytes are widely distributed throughout the dermis in dense sheets at the tumor stage⁶.

Many disorders can be considered differential diagnoses of classic MF, such as perioral dermatitis, seborrheic eczema, palmoplantar eczema, dyshidrotic eczema, atopic eczema, contact dermatitis, tinea corporis, tinea pedis, psoriasis, and parapsoriasis¹⁰.

Clinical variants

Hypopigmented MF

Hypopigmented MF is an uncommon clinical variant characterized by hypopigmented-to-achromic papules and macules without atrophy, sometimes with vitiligo-like lesions, in addition to patches ranging from small-size to large-size lesions^{8,11}.

Hypopigmented MF can be the only MF manifestation or coexist with classic MF lesions or other variants⁴. Lesions are mainly distributed on the trunk, extremities, and buttocks and may be associated with pruritus¹¹.

Hypopigmented MF is considered one of the commonly reported variants in children, although cases have been reported in adults too⁸. Dark-skinned individuals and Asians are commonly affected by hypopigmented MF^{4,8}. Despite it is believed to have no gender predilection, some studies observed remarkable female predominance¹¹.

The prognosis is typically excellent, at least compared to classic MF¹¹.

Table 1. The clinical, histological, and clinicopathologic variants of MF

Clinical variants
Hypopigmented MF
Erythrodermic MF
Papular MF and pityriasis lichenoides-like MF
Unilesional (solitary) MF
MF palmaris et plantaris
Ichthyosiform MF
Vegetating/papillomatous MF (acanthosis nigricans-like MF)
Erythema annulare centrifugum and erythema gyratum repens-like MF
Invisible MF
Clinicopathologic variants
Folliculotropic MF
Bullous and vesicular MF
Poikilodermatous MF
Pagetoid reticulosis (Woringer-Kolopp disease)
MF with eruptive infundibular (epidermoid) cysts
Syringotropic MF
Granulomatous slack skin
Hyperpigmented MF
Anetodermic MF
Verrucous MF
Psoriasiform MF
Dyshidrosis-like vesicular eruption
Pigmented purpuric dermatosis-like MF
Pustular MF
Histopathologic variants
Granulomatous MF
Interstitial MF
MF with large-cell transformation

Hypopigmented MF lesions are indistinguishable histopathologically from classic MF⁴. Some of the most common features include focal parakeratosis, lymphocytic infiltration in the upper dermis, slight or no spongiosis, and a variable number of lymphocytes at all levels of the viable epidermis disposed of as single units and episodically in small collections¹¹. Pautrier microabscesses are rarely observed¹¹. Other features involve slight psoriasiform epidermal hyperplasia, vacuolar alteration of the dermal-epidermal junction mimicking an interface dermatitis, scattered dyskeratotic keratinocytes, folliculotropism, and melanin incontinence associated with melanophages in the papillary dermis¹¹.

The differential diagnoses may include sarcoidosis, atopic dermatitis, leprosy, pityriasis alba, pityriasis versicolor, pityriasis lichenoides (PL) chronica, vitiligo, syphilis and other treponematoses, lichen sclerosus, postinflammatory hypopigmentation, idiopathic guttate hypomelanosis, onchocerciasis, hypomelanosis of Ito, and halo nevus¹¹.

Erythrodermic MF (EMF)

In erythrodermic MF (EMF), patients with the classic histopathologic findings of MF develop generalized erythroderma but with no diagnostic criteria of Sézary syndrome (SS), namely with the absence of blood involvement typical of SS^{2,8,12}. Additionally, they have a lower occurrence of lymphadenopathy¹². Anyway, SS is the main differential diagnosis of EMF⁸.

Generalized erythroderma is considered a progression of typical patch or plaque lesions of classic MF, but in some cases, erythroderma arises de novo^{2,12}. Pruritus is often present, and in rare cases, it may occur before the onset of the skin eruption¹².

Patients with EMF and Sézary syndrome had a poor overall prognosis¹², very particularly patients with erythroderma who have skin tumors¹².

Histopathological findings of EMF reveal classic features of MF with absent or a low amount of circulating neoplastic lymphocytes². However, epidermotropism is not present in some EMF cases¹².

Papular MF and pityriasis lichenoides-like MF

Pityriasis lichenoides-like MF (PL-like MF) is rare and occurs as a distinct variant of MF with a good prognosis presenting as localized or widespread erythematous scaly papules but without spontaneous regression of the lesions compared to PL^{4,13,14}. PL-like MF is commonly reported in young patients and less in adults and children^{4,13}.

Papular MF was primarily characterized in 2005 based on criteria including papules with histopathologic features of MF, spontaneous regression of lesions, and no additional evidence of lymphomatoid drug reaction or MF⁴. The prognosis is good in case there was no previous history of patches or any other clinical characteristics of MF; otherwise, the prognosis is bad if there is a previous history of patches or clinical features of MF¹³.

Papular MF lesions are presented as chronic and papular eruptions mainly located on the trunk and limbs with symmetric distribution¹³.

The histopathological findings of PL-like MF resemble both findings of MF (haloed lymphocytes, lymphocytes aligned along basal cells, Pautrier's microabscess, stuffed lymphocytes in the dermal papilla, coarse collagen bundles in the papillary dermis, and intraepidermal lymphocytes larger than dermal lymphocytes) and of PL (erythrocyte extravasation, spongiosis, necrotic keratinocytes, and exocytosis of lymphocytes and neutrophils)¹³. However, MF is distinguished from PL by the presence of epidermotropism and numerous atypical lymphocytes¹⁴.

The histopathological findings of papular MF do not comprise PL findings (such as necrotic keratinocytes or erythrocyte extravasation)¹³.

The differential diagnoses of PL-like MF include papular MF, PL, and lymphomatoid papulosis¹³, and the differential diagnoses of papular MF include, PL, lymphomatoid drug eruption, lymphomatoid papulosis type B, and persistent arthropod bite reactions⁴.

Unilesional MF

Unilesional MF, also known as solitary MF, presents as an isolated erythematous scaly patch or plaque generally located in sun-protected areas^{15,16}. Lesions grow slowly and may be present for several years without confirming the diagnosis^{4,16}. An excellent prognosis has been reported in previous studies⁷.

Unilesional MF is indiscernible histopathologically from the classic MF (patch and plaque-stage)⁷, but generally, atypia is more notable in the epidermotropic lymphocytes compared to those in the dermis⁷.

Unilesional follicular MF is a possibly curable form distinguished by neoplastic lymphocyte infiltration into the follicle¹⁷.

The main differential diagnosis of unilesional MF includes Bowen's disease, papulosquamous or eczematous lesions, and dermatophyte infection⁴.

Mycosis fungoides palmaris et plantaris (MFPP)

Mycosis fungoides palmaris et plantaris (MFPP) is a rare disorder expressed by erythematous hyperkeratotic patches or plaques with fissures and scales limited to palms or/and soles, often affected bilaterally, with or without itch, and without extracutaneous involvement^{4,18}. This variant can occur in classical MF patients (about 10% of the cases)⁴.

MFPP commonly presents in middle-aged individuals (16–68 years; mean age 55 years)¹⁸, occasionally with

pustular, vesicular, annular, verrucous, dyshidrotic, psoriasiform, hyperpigmented or ulcerative lesions, and nail dystrophy⁴.

Histopathological features are typical of MF, but spongiosis may be more distinct in MFPP, which makes it challenging to differentiate MFPP from spongiotic dermatitis⁴.

Differential diagnoses of MFPP may include palmo-plantar psoriasis, hand eczema, contact dermatitis, hyperkeratotic lichen planus, secondary syphilis, dermatophytosis, and verrucae¹⁸.

Ichthyosiform MF

Ichthyosiform MF is uncommon and generally presents as dry, diffuse, and scaling skin with well-circumscribed scaly patches or flat plaques, with a pattern resembling ichthyosis vulgaris's cobblestones^{4,8}. Lesions are typically located on the trunk and extremities and can be associated with other variants of MF, particularly FMF, or present only as ichthyosiform lesions^{4,19}. It has an indolent course and a favorable prognosis, with a mean age of onset is around 32 years¹⁹.

Ichthyosiform MF reveals compact orthokeratosis, hypogranulosis, and a band-like epidermotropic infiltrate comprised of small cerebriform lymphocytes⁹.

Many differential diagnoses can be taken into account, including ichthyosis vulgaris, drug eruption, sarcoidosis, underlying malignancy (such as paraneoplastic eruption), and endocrinologic and autoimmune disorders⁴.

Vegetating/papillomatous MF

Vegetating/papillomatous MF, also known as acanthosis nigricans-like MF, is a rare variant of MF that presents as brownish or velvety hyperpigmented, polygonal plaques with varying patches of erythema between the lesions located on the neck, axillae, groin, popliteal fossae, intergluteal, nipple, areolae, and periumbilical areas^{4,9,20}. Some lesions may become more prominent and even nodular²⁰. Lesions may be itchy^{4,9,20}.

Histopathologic features of acanthosis nigricans-like MF include the typical features of MF in addition to acanthosis and papillomatosis together with a band-like infiltrate of atypical lymphocytes that may be epidermotropic or not^{4,20}. Interconnected rete pegs and horny pseudocysts with seborrheic keratosis-like

features may be present⁴, which can mimic acanthosis nigricans or seborrheic keratosis based on their presentation, size, and color⁹.

Erythema annulare centrifugum (EAC) and erythema gyratum repens (EGR)-like MF

Many cases of MF with annular or polycyclic erythematous patches and/or plaques have been reported in the literature²¹. EAC-like MF is characterized by trailing scales and erythematous concentric rings, which expand outward without central clearing²¹, whereas EGR-like MF lesions are also characterized by symmetrically distributed red patches with erythematous concentric rings and trailing scales^{4,21}, but no evident central clearing, as the whole patch is comprised of band-like rings⁴.

Histopathologically, EAC-like MF has typical features of MF⁴ without the perivascular lymphocytic "coat-sleeve-like" infiltration typical of EAC⁴.

EAC-like MF may simulate Lyme disease, superficial fungal infection, and tinea imbricata^{4,21}.

Invisible MF

Invisible MF is an extremely rare variant that presents with persistent and occasionally generalized pruritus as the only clinical manifestation²²⁻²⁵ but has the histopathologic findings of classic MF²²⁻²⁵, including occasional Pautrier microabscesses^{23,25}.

Systemic amyloidosis, pseudoxanthoma elasticum, and pretibial myxedema has been reported in normal-looking skin, and they are considered differential diagnoses of invisible MF²².

Clinicopathologic variants

Folliculotropic MF (FMF)

Folliculotropic MF (FMF) is the most common atypical clinicopathologic variant^{1,4}. It is classified as a clinicopathological variant by WHO-EORTC classification that clarifies the existence of follicle-based lesions and folliculotropism as the predominant histopathological characteristics, with or without follicular mucinosis⁴.

FMF diagnosis comprises idiopathic follicular mucinosis, even though it is discussed whether this represents universal FMF or a distinct entity, and another entity that is amalgamated with CTCLs such as SS, MF, adult T-cell leukemia, and lymphomatoid papulosis²⁶.

The clinical presentation of FMF includes various morphologies such as erythematous plaques, follicular

papules, acneiform lesions, prurigo-like lesions, cysts, and patches of alopecia that can associate with eyebrow involvement and maybe with scarring^{6,27,28}, in addition to other unusual presentations that include pseudotumors, rosacea-like lesions, lupus tumidus-like, and lichen spinulosus-like lesions in association with alopecia and hypopigmentation²⁸. Alopecia is a common and typical featured finding of FMF which is observed in up to 81% of patients²⁸. Lesions are located mainly on the upper trunk and extremities (in up to 73% of patients), neck, and face²⁷, very often reported as predilection locations²⁶. Leonine appearance is a rare expression of MF, which is associated with stage-IV CTCL and with blood and folliculotropism involvement during the disease progression^{26,27}.

Difficult-to-manage pruritus is a common symptom in adult patients, but in contrast, children with FMF complain of mild pruritus²⁶. FMF mainly affects adults but has also been reported in adolescents and children with a male predominance^{4,26}.

Erythroderma also may manifest in up to 6% of FMF cases²⁶. 92% of patients have skin-restricted involvement, while 8% of them have visceral or nodal involvement at their first presentation²⁸. Secondary bacterial infections are commonly noticed in FMF patients¹.

FMF is characterized histopathologically by infiltration of atypical lymphocytes surrounding the hair follicles and generally spares the interfollicular epidermis and is occasionally accompanied by the follicle's disruption^{4,27}. A mild perivascular inflammatory infiltrate occurs in the upper dermis without evident lymphocyte atypia in the early stage^{27,28}, and apart from follicles, infiltration can also affect eccrine sweat glands (syringotropism): adnexotropic MF¹. In addition, mucin degeneration of the follicular epithelium was typically reported in many cases^{1,27}.

The most paramount histopathological differential diagnoses of FMF include pseudolymphomatous folliculitis, follicular lymphomatoid papulosis, and follicular eczema²⁶.

FMF diagnosis may be delayed, 18–48 months on average, after the lesion onset due to its distinct clinical presentation of classic MF^{26,28}.

Recent studies classified an early-stage FMF with a good prognosis and a more aggressive advanced-stage FMF subgroup²⁶, which has a poor prognosis with a 5-year surviving rate of 70–80%²⁷. The survival range of tumor FMF is similar to classical tumor-stage MF⁴. Reduced survival has been linked to large cell transformation, advanced age, and broad secondary bacterial infection¹.

Differential diagnoses depend upon the various clinical presentations of FMF⁴. Erythematous lesions on the scalp can be misdiagnosed as psoriasis capitis, atopic dermatitis, and seborrheic dermatitis⁴. Alopecia on the scalp can mimic trichotillomania, cicatricial alopecia, and alopecia areata⁴. Rosacea, adult-onset acne, follicular-comedogenic graft-versus-host disease, chloracne, and Favre-Racouchot syndrome have to differentiate from acneiform lesions⁴. Pityriasis rubra pilaris, lichen spinulosus, lichen planopilaris, and keratosis pilaris should be taken into account as differential diagnoses in follicular spiky papules⁴. In addition, alopecia mucinosa should be considered as a differential diagnosis in hairless patches and/or plaques⁴.

Bullous and vesicular MF

Bullous and vesicular MF, also known as vesiculobullous MF lesions, are rare and aggressive variants of MF that can occur on normal-appearing skin and/or on the affected skin with classic MF/SS^{4,29}. Vesiculobullous MF lesions usually manifest as multiple flaccid or tense bullae on the trunk and proximal limbs with a predisposition to form ulcers^{4,6,29,30}. The lesions have a poor prognosis and mostly affect older people without gender predominance²⁹.

Has been reported; an association between bullous MF, bullous pemphigoid, former treatment with psoralen plus ultraviolet A, topical mechlorethamine, or/and systemic interferon^{4,29}. In addition, it is very probable that vesicular MF can onset on the affected skin with atopic diathesis⁵.

The histopathological mechanism underlying blister formation has not been demonstrated²⁹. The confluence of malignant lymphocytes within the epidermis causes the secession of the epidermis from the dermis⁵.

Vesiculobullous MF lesions are expressed by intraepidermal or subepidermal blisters combined with classic findings of MF like atypical lymphocytes, epidermotropism, and the aggregation of Pautrier's microabscesses^{5,8,29}.

Bullous MF can mimic many disorders, including autoimmune bullous disorders (bullous pemphigoid, bullous lichen planus, bullous lupus erythematosus, and pemphigus vulgaris), porphyria, drug eruptions, and viral infections^{4,6,29}. Besides, vesicular MF should be differentiated from autoimmune bullous disorders, eczematous dermatitis, bacterial or viral infections, and drug eruption⁴. However, vesiculobullous MF lesions are distinguished from blistering autoimmune diseases by their negative direct and indirect immunofluorescence results⁸.

Poikilodermatous MF

Poikilodermal MF, also known as poikiloderma vasculare atrophicans, is a variant of MF, that is characterized by cutaneous atrophy, macular pigmentary changes, mild scaling, and telangiectasia^{4,8,31}. It is usually considered a clinicopathologic variant of patch-stage classic MF⁴.

Poikilodermal MF manifests as small plaques or papules, usually asymptomatic or mildly pruritic, ordered in a net-like pattern at the onset of the lesions, then the lesions usually develop into large plaques or affect the skin generally³¹. However, the lesions are typically either stable or slowly expanding³¹.

The most common locations of poikilodermatous MF are the breast (in women) and buttocks (in both women and men)⁸. The skin of the patient may resemble "cigarette paper" as a result of atrophy and thinning³¹.

Poikilodermatous MF has been reported in children with a higher percentage compared to adults¹⁵. Also, there have been reports of progression from poikilodermal MF in childhood to EMF in adulthood¹⁵. Anyhow, the prognosis of poikilodermal MF is favorable, and it responds to phototherapy⁸.

Histopathologically, poikilodermal MF shows an atypical T-cell infiltrate in the papillary dermis, often with obvious epidermotropism³¹. In addition, melanophages and melanin incontinence are present, associated with ectasia of the superficial dermal vessels and epidermal atrophy³¹. Pautrier microabscesses are not typically present⁸.

Morphea, lichen sclerosus, ashy dermatosis, and radiation dermatitis are considered differential diagnoses of poikilodermal MF⁴.

Pagetoid reticulosis (PR)

Pagetoid reticulosis (PR), also known as Woringer-Kolopp disease, is a rare variant of MF occurring both in children and adults^{4,6}. It typically manifests as a slowly progressive, solitary, hyperkeratotic or psoriasiform patch or plaque with a well-defined elevated border and a central clearing that usually affects the limbs, especially the feet and hands^{1,6}. In some cases, ulceration and pain were also reported⁶.

PR has an excellent prognosis with no disease-related deaths or extracutaneous involvement¹.

However, PR may progress to a disseminated PR or Ketrion-Goodman disease, which currently corresponds to a more aggressive form of cutaneous lymphoma (epidermotropic cytotoxic T-cell lymphoma in almost all reported cases)⁸.

Typical histopathologic findings of PR include epidermal hyperplasia and marked infiltration by small to

medium-sized atypical pagetoid cells, ordered separately or in nests or clusters¹. Atypical cells consist of medium to large-sized cerebriform nuclei with abundant, vacuolated cytoplasm¹. Neoplastic T-cells are rarely observed in the superficial dermis, but an infiltration mostly of small lymphocytes can occur¹.

The differential diagnoses of PR may involve psoriasis, chronic dermatitis, verrucous squamous cell carcinoma, tuberculosis verrucosa cutis, and blastomycosis⁴.

Mycosis fungoides (MF) with eruptive infundibular (epidermoid) cysts

Some MF patients have reported having a localized or generalized follicular eruption with comedones and infundibular cysts, which appears to be a rare variant of MF⁸. This form combines MF with multiple, tiny, and eruptive epidermoid cysts and comedones³². Keratinous cysts can occur on uninvolved skin or on MF patches and plaques³². Some lesions have an acne-like or comedo-like manifestation³². Lesions may occasionally resemble tumor-stage lesions due to their size and inflammatory appearance⁸.

MF with eruptive infundibular cysts needs to be differentiated from FMF, although some authors consider these two variants are part of the same spectrum with follicular involvement in MF⁸. Also, Favre-Racouchot disease should be considered as a differential diagnosis if MF with eruptive infundibular cysts lesions are located on the face³².

Histopathology shows the characteristic features of an infundibular cyst encompassed by a dense infiltrate formed mainly by atypical lymphocytes in the cyst wall⁸. Infundibular cysts may be associated with the infiltration of follicular openings by neoplastic cells, causing expansion of the infundibula and subsequent blockage⁸.

Syringotropic MF (STMF)

Syringotropic MF (STMF) is a rare variant of MF characterized by eccrine sweat gland infiltration^{1,4}. It is also called syringotropic CTCL, syringolymphoid hyperplasia with alopecia, or adnexotropic T-cell lymphoma⁴. STMF features imbricate with FMF and, therefore, it was classified as a subtype of FMF within the WHO-EORTC classification⁴, but differences in survival between STMF and FMF in a recent study suggested they should be categorized separately³³. STMF is much less aggressive than FMF³⁴.

STMF is usually located in sun-protected areas with a tendency to affect males twice as often as females,

with a mean age of 55^{4,34}. It presents as a solitary lesion or numerous erythematous patches, papules, or plaques with dotted follicular accentuation, in addition to overlying alopecia, which is reported commonly in STMF^{4,34}. Also, hypohidrosis is periodically observed in STMF³⁴.

STMF demonstrates histopathological features, including hyperplasia of eccrine glands and ducts encompassed and penetrated by dense infiltration of atypical lymphocytes in the dermis³⁴.

The differential diagnoses of STMF involve perniosis, neutrophilic eccrine hidradenitis, classic MF, and syringometaplasia without a significant lymphocytic infiltrate, as in post-chemotherapy, ischemia, and radiation dermatitis³⁵.

Granulomatous slack skin (GSS)

Granulomatous slack skin (GSS) is a very rare clinicopathologic variant of MF that shares histopathological characteristics with granulomatous MF (GMF), which makes it difficult to differentiate it from this variant^{1,6}. It is more common in younger people⁶.

Initial cutaneous lesions in GSS have a similar presentation to classic MF, including patches and plaques¹. Then GSS lesions develop into large and pendulous folds of atrophic skin, due to the loss of elastic fibers, in locations such as groins and axilla (flexural areas) resembling cutis laxa^{1,2}. Extracutaneous involvement of GSS is uncommon⁶. Hodgkin lymphoma or nodal non-Hodgkin lymphoma has been reported as an associated disease in 30–50% of GSS cases².

GSS is manifested by a slow and indolent advanced clinical course¹. However, the complete recovery of GSS has never been reported¹.

Histopathology of GSS includes multinucleated giant cells (comprising > 10 nuclei for each cell) in addition to elastophagocytosis, emperipolesis (engulfment of lymphocytes), and loss of elastic tissue¹. The infiltration by small atypical T-cells with cerebriform nuclei in the epidermis may be observed, as in the classic MF¹.

It is necessary to take into account differential diagnoses such as infectious granulomas, sarcoidosis, granuloma annulare, and anetodermic MF (AMF)^{36,37}.

Hyperpigmented MF

Hyperpigmented MF is a very rare variant of MF classified as an unusual clinical manifestation of palmaris et plantaris MF and presents clinically as hyperpigmented macules, patches, and/or plaques without

the presence of poikilodermatous changes^{4,8,38}. Some cases manifest with indistinct borders and diverse degrees of skin atrophy and scaling⁴.

Although some patients may present with associated lesions of classic MF or other MF variants, hyperpigmented MF may be the only manifestation of MF⁴.

Hyperpigmented MF typically affects people with dark skin and younger ages (under 35 years old), and it has slowed clinical progression³⁸. Anyhow, it has a better prognosis compared to classic MF³⁸.

Histopathologically, in addition to findings of classic MF, diffuse vacuolar degeneration of basal keratinocytes imitating "interface dermatitis", along with melanophages, have been observed in the most hyperpigmented MF cases⁴.

Many disorders should be considered as differential diagnoses of hyperpigmented MF, including pigmented contact dermatitis, cutaneous amyloidosis, fixed drug eruption, post-inflammatory hyperpigmentation, idiopathic eruptive macular hyperpigmentation, atrophoderma of Pasini and Pierini, and erythema dyschromicum perstans⁴.

Anetodermic MF (AMF)

Anetodermic MF (AMF) is a cutaneous disorder characterized by progressive loss of dermal elastic tissue, which results in atrophic plaques with a featured parchment-like surface⁸. The most involved locations are limbs, face, buttocks, and trunk³⁷.

Primary anetoderma occurs when there is no underlying associated disease, and it arises on clinically normal skin, whereas secondary anetoderma appears on the same site as a prior specific skin lesion³⁷. However, the appearance of AMF in classic MF lesions is extremely rare⁸.

Histopathologically, T-helper lymphocytes are infiltrated into the dermis with a few histiocytes and some multinucleate large cells engulfing deformed elastic fibers³⁷. In the dermis, elastic fibers are almost completely absent³⁷.

GSS is the main differential diagnosis of AMF³⁷.

Verrucous MF

Verrucous MF is a quite rare variant of MF which presents as warty, hyperkeratotic, pruritic plaques that can be located on the trunk, face, and limbs and can be associated with classic MF lesions⁴.

Verrucous MF lesions may manifest as single or many erythematous papules that progressively enlarge

and become more raised with a verrucous surface³⁹. Apart from pruritus, most verrucous MF lesions are asymptomatic³⁹.

Location on the extremities was commonly reported in African-Americans with a history of long-standing MF³⁹. It has been noticed that African-American women are more likely to develop early-onset MF with a poor prognosis³⁹.

Histopathologic characteristics of verrucous MF involve classic MF findings along with hyperkeratosis and papillomatosis, inflammatory infiltration into the papillary dermis, and exocytosis and spongiosis in the epidermis⁸.

Many disorders can be assumed as differential diagnoses, such as verrucae vulgaris, keratoacanthoma, palmoplantar hyperkeratosis, seborrheic keratosis, porokeratosis of Mibelli, and inflammatory linear verrucous epidermal nevus⁴.

Psoriasiform MF

Psoriasiform MF is a rare variant of MF considered an unusual clinical manifestation of palmaris et plantaris^{4,40}.

The clinical presentation of psoriasiform MF involves scaly, well-defined, thick, erythematous psoriasiform plaques, which can mimic psoriasis⁴. Additional alopecia, induration, erosions, and ulcerative lesions may occur in some patients⁴. However, many cases reported generalized lesions^{40,41}.

The majority of reported cases were in males, with a mean age of 54 years⁴¹.

Histopathological findings are characterized by epidermotropism of atypical lymphocytes⁴⁰. Scant spongiosis and a lichenoid pattern have also been reported⁴. In addition, histopathologic findings of psoriasis, including elongation of the rete ridges with regular acanthosis, thinning, parakeratosis with hyperkeratosis, or Munro microabscesses and total effacement of the granular layer are present⁴².

The clinical differential diagnoses of psoriasiform MF include psoriasis vulgaris, lichen planus, lichen simplex chronicus, leprosy, and ashy dermatosis⁴⁰.

Dyshidrosis-like vesicular eruption (DLVE)

Dyshidrosis-like vesicular eruption (DLVE) is an extremely rare variant of MF³⁰. It presents as vesicles restricted to palms and soles with a possible expansion to the trunk and extremities, but there have been no

reported cases of extracutaneous involvement³⁰. DLVE has been reported in association with adult T-cell lymphoma/leukemia³⁰.

The microscopic sections show typical features of MF, including cerebriform lymphocytes, epidermotropic lymphocytes, and Pautrier microabscesses³⁰. In addition, lymphokines released by neoplastic T-cells might obstruct normal keratinocyte adhesion³⁰. Immunofluorescence studies of DLVE are negative, but acantholysis may occur³⁰.

Contact dermatitis, atopic eczema, and palmoplantar eczema are considered differential diagnoses of DLVE⁶.

Pigmented purpuric dermatosis (PPD)-like MF

Pigmented purpuric dermatosis (PPD)-like MF is considered a rare variant of MF⁴. It is usually reported in children and adults with a male predilection^{4,43}. PPD-like MF is characterized by golden-brown discoloration and enduring purpuric lesions⁴. It can mimic chronic pigmented purpura clinically⁴. The most common location of PPD-like MF is the lower extremities, with a rare possibility of a generalized involvement⁴³. The histopathological examination of PPD-like MF reveals similar characteristics of MF, besides extravasation of erythrocytes in the papillary dermis with the presence of siderophages⁴.

Pustular MF

Pustular MF is a very rare variant of MF which is considered an unusual manifestation of palmaris et plantaris MF⁴. It is characterized as a persistent vesicular pustular eruption that gradually transforms into typical MF plaques⁸. Anyway, the pustular MF lesions can be generalized or restricted to the palmoplantar location⁸.

Histopathology reveals typical MF findings, such as epidermotropism, band-like infiltration of atypical lymphocytes, and Pautrier microabscesses, in amalgamation with neutrophils, eosinophils, subcorneal pustules containing atypical lymphocytes⁸.

Pustular psoriasis, drug reaction, and skin infections are considered differential diagnoses of pustular MF⁴.

Histopathologic variants

Granulomatous MF (GMF)

Granulomatous MF (GMF) is a histopathological variant of MF that may be diagnosed at the time of its first

onset or years later⁴. It may manifest clinically as papules, plaques, or ulcerated nodules, without the characteristics of a cutis laxa-like that are typical of GSS^{4,44}. GMF occurs more frequently in males in their 5th and 6th decades of life⁴⁴.

GMF progresses frequently and is associated with a high risk of developing a second lymphoma⁸. In addition, its prognosis is poorer than classic MF⁸.

The EORTC's histopathologic criteria for GMF involve a histiocyte-rich infiltrate with histiocytes accounting for > 25% of the whole infiltrate, prominent granuloma formation, or a large number of histiocytic giant cells⁴. GMF has a variety of histopathologic patterns, including epithelioid, sarcoidal, palisaded, periadnexal, tuberculoid, necrobiotic granuloma-like, granuloma annulare-like, and diffuse granulomatous infiltrate⁴.

Although GMF is clinically distinct from GSS, histopathologic examination reveals a decreased portion of multinucleated cells⁸. Epidermotropism is typically not a prominent feature². Also, elastophagocytosis is a rare finding, but the loss of elastic fibers is common⁴.

The differential diagnoses of GMF include lipoid necrobiosis, annular granuloma, granulomatous panniculitis, and granulomatous rosacea⁴⁴.

Interstitial MF

Interstitial MF lesions are a rare histopathologic manifestation of MF, with a persistent cytotoxic phenotype⁴⁵. Patches and plaques are the typical clinical exhibition of interstitial MF, which can arise at any location of the body, in addition to atrophy and lack of scales^{4,45,46}. The lesions can also present as erythematous patches surrounding the nasolabial folds and small papules located on the chin, which are called perioral dermatitis-like lesions⁴⁷.

Histopathologically, distinguishing features of interstitial MF include lymphocytes infiltrating the dermis and dissecting the collagen bundles⁴. Epidermotropic lymphocytes present focally in many cases⁴. Additionally, mucin deposition may present in the dermis⁸. However, the histopathological features of interstitial MF correspond to the interstitial variant of granuloma annulare⁴⁸.

The main differential diagnoses of IMF include interstitial granuloma annulare, interstitial granulomatous dermatitis, and the inflammatory stage of morphea^{4,45}. Moreover, the differential diagnoses regarding perioral dermatitis-like lesions include contact dermatitis, seborrheic eczema, and atopic eczema⁶.

Table 2. The most involved areas, the typical clinical presentation, and clinical differential diagnoses/mimickers of MF variants

MF variants	The most involved locations	The clinical presentation	Clinical differential diagnoses
Classic MF	Sun-protected areas (breast in females), buttocks, trunk, and extremities.	Patch-stage: asymmetric telangiectasias and erythematous macules. Plaque-stage: erythematous, reddish-brown, scaling lesions. Tumor-stage: nodules ≥ 1 cm.	Perioral dermatitis, seborrheic eczema, palmoplantar eczema, dyshidrotic eczema, atopic eczema, contact dermatitis, tinea corporis, tinea pedis, psoriasis, and parapsoriasis.
Hypopigmented MF	Trunk, extremities, and buttocks.	Hypopigmented-to-achromic papules, macules without atrophy, vitiligo-like lesions, small to large-size patches.	Sarcoidosis, atopic dermatitis, leprosy, pityriasis alba, pityriasis versicolor, pityriasis lichenoides chronica, vitiligo, syphilis and other treponematoses, lichen sclerosus, postinflammatory hypopigmentation, idiopathic guttate hypomelanosis, onchocerciasis, hypomelanosis of Ito, and halo nevus.
Erythrodermic MF	Generalized	A progression from a typical patch or plaque lesions of classic MF, but the lesions can also arise de novo.	Sézary syndrome.
Papular MF and pityriasis lichenoides (PL)-like MF	Trunk and extremities.	Papular MF: chronic and symmetrically scattered papular eruptions. PL-like MF: localized or widespread erythematous scaly papules.	Papular MF: PL, lymphomatoid drug eruption, lymphomatoid papulosis type B, and persistent arthropod bite reactions. PL-like MF: papular MF, PL, and lymphomatoid papulosis.
Unilesional (solitary) MF	Sun-protected areas.	Isolated erythematous scaly patch or plaque.	Bowen's disease, papulosquamous or eczematous lesions, and dermatophyte infection.
MF palmaris et plantaris	Palms and soles.	Erythematous hyperkeratotic patches or plaques.	Palmoplantar psoriasis, hand eczema, contact dermatitis, hyperkeratotic lichen planus, secondary syphilis, dermatophytosis, and verrucae.
Ichthyosiform MF	Trunk and extremities.	Dry, diffuse, and scaling skin with well-circumscribed scaly patches or flat plaques.	Ichthyosis vulgaris, drug eruption, sarcoidosis, underlying malignancy (such as paraneoplastic eruption), Infectious diseases, and endocrinologic and autoimmune disorders.
Vegetating/papillomatous MF (acanthosis nigricans-like MF)	Neck, axillae, groin, popliteal fossae, inter-gluteal, nipple, areolae, and peri-umbilical areas.	Brownish or velvety hyperpigmented, polygonal plaques with varying patches of erythema scattered between the lesions.	Acanthosis nigricans and seborrheic keratosis.
Erythema annulare centrifugum (EAC) and erythema gyratum repens (EGR)-like MF	Not enough available data.	EAC-like MF: trailing scales and erythematous concentric rings. EGR-like MF: symmetrically distributed red patches with erythematous concentric rings and trailing scales.	EAC-like MF: Lyme disease, superficial fungal infection, and tinea imbricata.
Invisible MF	Some cases reported generalized pruritus as the only manifestation of this variant.	No visible dermatoses.	Systemic amyloidosis, pseudoxanthoma elasticum, and pretibial myxedema.

(Continues)

Table 2. The most involved areas, the typical clinical presentation, and clinical differential diagnoses/mimickers of MF variants (*continued*)

MF variants	The most involved locations	The clinical presentation	Clinical differential diagnoses
Folliculotropic MF	Trunk, extremities, head, neck, and face.	Erythematous plaques, follicular papules, acneiform lesions, prurigo-like lesions, and cysts.	Erythematous lesions on the scalp: psoriasis capitis, atopic dermatitis, and seborrheic dermatitis. Alopecic lesions on the scalp: trichotillomania, cicatricial alopecia, and alopecia areata. Acneiform lesions: rosacea, adult-onset acne, follicular-comedogenic graft-versus-host disease, chloracne, and Favre-Racouchot syndrome. Follicular spiky papules: pityriasis rubra pilaris, lichen spinulosus, lichen planopilaris, and keratosis pilaris. Hairless patches and/or plaques: alopecia mucinosa.
Bullous/vesicular MF	Trunk and proximal extremities.	Flaccid or tense bullae with a predisposition to form ulcers.	Bullous MF: autoimmune bullous disorders (bullous pemphigoid, bullous lichen planus, bullous lupus erythematosus, and pemphigus vulgaris), porphyria, drug eruptions, and viral infections. Vesicular MF: autoimmune bullous disorders, eczematous dermatitis, bacterial or viral infections, and drug eruption.
Poikilodermatous MF	Breast (in women) and buttocks (in both women and men).	Small plaques or papules are ordered in a net-like pattern, cutaneous atrophy, macular pigmentary changes, mild scaling, and telangiectasia.	Morphea, lichen sclerosus, ashy dermatosis, and radiation dermatitis.
Pagetoid reticulosis (Woringer-Kolopp disease)	Extremities (especially the feet and hands).	Solitary, hyperkeratotic or psoriasiform patch or plaque with a well-defined elevated border and a centric clearing.	Psoriasis, chronic dermatitis, verrucous squamous cell carcinoma, tuberculosis verrucosa cutis, and blastomycosis.
MF with eruptive infundibular (epidermoid) cysts	Not enough available data.	Localized or generalized follicular eruption with comedones and infundibular cysts.	Folliculotropic MF and Favre-Racouchot disease.
Syringotropic MF	Sun-protected areas.	Solitary lesions or numerous erythematous patches, papules, or plaques with dotted follicular accentuation.	Perniosis, neutrophilic eccrine hidradenitis, classic MF, and syringometaplasia without a significant lymphocytic infiltrate (as in post-chemotherapy, ischemia, and radiation dermatitis).
Granulomatous slack skin	Flexural areas.	Initial lesions have a similar presentation to classical MF, including patches and plaques.	Infectious granulomas, sarcoidosis, granuloma annulare, and anetodermic MF.
Hyperpigmented MF	Not enough available data.	Hyperpigmented macules, patches, and/or plaques without the presence of poikilodermatous changes.	Pigmented contact dermatitis, cutaneous amyloidosis, fixed drug eruption, post-inflammatory hyperpigmentation, idiopathic eruptive macular hyperpigmentation, atrophoderma of Pasini and Pierini, and erythema dyschromicum perstans.
Anetodermic MF	Extremities, face, buttocks, and trunk.	Atrophic plaques with a featured parchment-like surface.	Granulomatous slack skin.
Verrucous MF	Trunk, face, and extremities.	Single or many erythematous papules with a verrucous surface.	Verrucae Vulgaris, keratoacanthoma, palmoplantar hyperkeratosis, seborrheic keratosis, porokeratosis of Mibelli, and inflammatory linear verrucous epidermal nevus.

(Continues)

Table 2. The most involved areas, the typical clinical presentation, and clinical differential diagnoses/mimickers of MF variants (*continued*)

MF variants	The most involved locations	The clinical presentation	Clinical differential diagnoses
Psoriasiform MF	Many cases reported a generalized presentation of the lesions.	Scaly, well-defined, thick, erythematous psoriasiform plaques.	Psoriasis vulgaris, lichen planus, lichen simplex chronicus, leprosy, and ashy dermatosis.
Dyshidrosis-like vesicular eruption	Palms and soles.	It presents as vesicles.	Contact dermatitis, atopic eczema, and palmoplantar eczema.
Pigmented purpuric dermatosis-like MF	Lower extremities.	Golden-brown discoloration and enduring purpuric lesions.	Chronic pigmented purpura.
Pustular MF	Generalized or restricted to the palmoplantar location.	A persistent vesicular pustular eruption.	Pustular psoriasis, drug reaction, and skin infections.
Granulomatous mycosis fungoides	Not enough available data.	Papules, plaques, or ulcerated nodules.	Lipoid necrobiosis, annular granuloma, granulomatous panniculitis, and granulomatous rosacea.
Interstitial MF	Interstitial MF: any location of the body. Perioral dermatitis-like lesions: surrounding the nasolabial folds and on the chin.	Interstitial MF: patches, plaques, atrophy, and lack of scales. Perioral dermatitis-like lesions: patches and small papules.	Interstitial MF: granuloma annulare, interstitial granulomatous dermatitis, and the inflammatory stage of morphea. Perioral dermatitis-like lesions: contact dermatitis, seborrheic eczema, and atopic eczema.

Mycosis fungoides (MF) with large-cell transformation (LCT)

The development of large T-cell lymphoma from MF is classified as a histopathologic variant of MF which is described as the exhibition of large cells (> 4 times the size of a small lymphocyte) in at least 25% of the dermal infiltrate or forming microscopic nodules in which large cells that are either CD30⁺ or CD30⁻^{8,49}.

Mycosis fungoides (MF) with large-cell transformation (MF-LCT) is commonly present with a poor prognosis and arises in 20-50% of advanced MF⁵⁰. However, it occurs more frequently in tumor-stage MF patients⁸.

MF-LCT must be differentiated from other essential cutaneous lymphomas with CD30⁺ large cells, like lymphomatoid papulosis and anaplastic large-cell lymphoma⁸. Anyway, the prognosis for MF-LCT is poor, while the prognosis for cutaneous anaplastic large-cell lymphoma is excellent⁴⁹.

Epidermal hyperplasia and dermal fibrosis at transformation were linked to longer survival⁵⁰. On the other hand, the shorter survival appears to be correlated with a clinically advanced stage at transformation, older age, and serum lactate dehydrogenase of > 220 U/L⁵⁰. A recent study suggests that patients with MF who have CD30⁺ large-cell tumors have a better prognosis than those with CD30⁻ large-cell tumors⁴⁹.

A summary of the most involved locations, clinical presentations, and differential diagnoses of MF variants are demonstrated in the following (Table 2)^{1,2,4-13,15,16,18-47}.

Conclusion

The variants of MF exhibit a wide range of clinical and histopathologic manifestations, which can mimic a broad spectrum of benign inflammatory skin diseases either clinically, histopathologically, or clinicopathologically. Therefore, the diagnosis of MF variants may be challenging. High awareness of MF clinical manifestations, in addition to histopathologic correlation along with the immunophenotypical studies, are required to obtain the correct diagnosis of MF.

Authors' contributions

Jacob Al-Dabbagh: wrote and edited the manuscript, performed the literature review, and revised the final manuscript. Nemat Ismail, Moath Alsleman, and Eman Mohammad Deeb: performed the literature review, and participated in revising the manuscript. Lina Al-Soufi: the mentor, and reviewed the article. Zuheir Al-Shehabi: the guarantor, and revised the manuscript.

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Conflicts of interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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References

- Willemze R. Mycosis fungoides variants-clinicopathologic features, differential diagnosis, and treatment. *Semin Cutan Med Surg.* 2018;37:11-17.
- Mahalingam M, Reddy VB. Mycosis fungoides, then and now... have we travelled? *Adv Anat Pathol.* 2015;22:376-83.
- Agbai ON, Buster K, Sanchez M, Hernandez C, Kundu RV, Chiu M, et al. Skin cancer and photoprotection in people of color: a review and recommendations for physicians and the public. *J Am Acad Dermatol.* 2014;70:748-62.
- Hodak E, Amitay-Laish I. Mycosis fungoides: a great imitator. *Clin Dermatol.* 2019;37:255-67.
- Montahen S, Nuovo GJ, Magro CM. Vesicular mycosis fungoides. *Am J Dermatopathol.* 2015;37:724-9.
- Alsayyah A. Is it mycosis fungoides? A comprehensive guide to reaching the diagnosis and avoiding common pitfalls. *Ann Diagn Pathol.* 2020;47:151546.
- Ally MS, Pawade J, Tanaka M, Morris S, Mitchell T, Child F, et al. Solitary mycosis fungoides: a distinct clinicopathologic entity with a good prognosis: a series of 15 cases and literature review. *J Am Acad Dermatol.* 2012;67:736-44.
- Muñoz-González H, Molina-Ruiz AM, Requena L. Clinicopathologic variants of mycosis fungoides. *Actas Dermosifiliogr.* 2017;108:192-208.
- Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. *J Eur Acad Dermatol Venereol.* 2004;18:397-415.
- Nashan D, Faulhaber D, Ständer S, Luger TA, Stadler R. Mycosis fungoides: a dermatological masquerader. *Br J Dermatol.* 2007;156:1-10.
- Furlan FC, Sanches JA. Hypopigmented mycosis fungoides: a review of its clinical features and pathophysiology. *An Bras Dermatol.* 2013;88:954-60.
- Kamijo H, Sugaya M. Two distinct variants of mycosis fungoides (MF): folliculotropic MF and erythrodermic MF. *J Dermatol.* 2019;46:1136-40.
- Jang MS, Kang DY, Park JB, Kim JH, Park KA, Rim H, et al. Pityriasis lichenoides-like mycosis fungoides: clinical and histologic features and response to phototherapy. *Ann Dermatol.* 2016;28:540-7.
- Cho EB, Youn SH, Park EJ, Kwon IH, Kim KH, Kim KJ. CD8-positive pityriasis lichenoides-like mycosis fungoides. *Eur J Dermatol.* 2012;22:415-6.
- Wu JH, Cohen BA, Sweren RJ. Mycosis fungoides in pediatric patients: clinical features, diagnostic challenges, and advances in therapeutic management. *Pediatr Dermatol.* 2020;37:18-28.
- Kaufmann F, Kettelhack N, Hilty N, Kempf W. Unilesional plantar mycosis fungoides treated with topical photodynamic therapy - case report and review of the literature. *J Eur Acad Dermatol Venereol.* 2017;31:1633-7.
- Magro CM, Telang GH, Montahen S. Unilesional follicular mycosis fungoides: report of 6 cases and review of the literature. *Am J Dermatopathol.* 2018;40:329-36.
- Kim ST, Jeon YS, Sim HJ, Kim SH, Kim YK, Suh KS, et al. Clinicopathologic features and T-cell receptor gene rearrangement findings of mycosis fungoides palmaris et plantaris. *J Am Acad Dermatol.* 2006;54:466-71.
- Pereira LB, Sobreira NP, Rocha VB. Case for diagnosis. Ichthyosiform mycosis fungoides. *An Bras Dermatol.* 2022;97:795-7.
- Kim DJ, Truong SV, Paik A, Kraus C, Harris RM, Barr RJ, et al. A case of acanthosis nigricans-like mycosis fungoides. *JAAD Case Rep.* 2021;16:144-8.
- Notay M, Petukhova TA, Kiuru M, Kunder CA, Hwang ST. Mycosis fungoides presenting as symmetric concentric patches mimicking figurate erythema. *JAAD Case Rep.* 2017;3:288-90.
- Pujol RM, Gallardo F, Llistosella E, Blanco A, Bernadó L, Bordes R, et al. Invisible mycosis fungoides: a diagnostic challenge. *J Am Acad Dermatol.* 2000;42:324-8.
- Deen K, O'Brien B, Wu J. Invisible mycosis fungoides: not to be missed in chronic pruritus. *Dermatol Ther (Heidelb).* 2015;5:213-6.
- Hwang H, Nichols T, Duvic M. "Invisible" mycosis fungoides? *J Am Acad Dermatol.* 2001;45:318.
- Pujol RM, Gallardo F, Llistosella E, Blanco A, Bernadó L, Bordes R, et al. Invisible mycosis fungoides: a diagnostic challenge. *J Am Acad Dermatol.* 2000;42:324-8.
- Mitteldorf C, Stadler R, Sander CA, Kempf W. Folliculotropic mycosis fungoides. *J Dtsch Dermatol Ges.* 2018;16:543-557.
- Malveira MIB, Pascoal G, Gamonal SBL, Castañón MCMN. Folliculotropic mycosis fungoides: challenging clinical, histopathological and immunohistochemical diagnosis. *An Bras Dermatol.* 2017;92:73-5.
- Tambe SA, Zambare US, Nayak CS. Folliculotropic mycosis fungoides. *Indian Dermatol Online J.* 2021;12:178-80.
- Kneitz H, Bröcker EB, Becker JC. Mycosis fungoides bullosa: a case report and review of the literature. *J Med Case Rep.* 2010;4:78.
- Diehl J, Sarantopoulos GP, Chiu MW. Dysidrotic mycosis fungoides. *J Cutan Pathol.* 2011;38:590-2.
- Pankratov O, Gradova S, Tarasevich S, Pankratov V. Poikilodermatous mycosis fungoides: clinical and histopathological analysis of a case and literature review. *Acta Dermatovenereol Alp Pannonica Adriat.* 2015;24:37-41.
- Aloi F, Tomasini C, Pippione M. Mycosis fungoides and eruptive epidermoid cysts: a unique response of follicular and eccrine structures. *Dermatology.* 1993;187:273-7.
- Echols KF, Bressler L, Armeson K, Maize JC Sr. Syringotropic mycosis fungoides: a variant of folliculotropic mycosis fungoides or a distinct entity? *Am J Dermatopathol.* 2019;41:807-9.
- Lehmer LM, Amber KT, de Feraudy SM. Syringotropic mycosis fungoides: a rare form of cutaneous t-cell lymphoma enabling a histopathologic "sign of relief." *Am J Dermatopathol.* 2017;39:920-3.
- Virmani P, Myskowski PL, Pulitzer M. Unusual variants of mycosis fungoides. *Diagn Histopathol (Oxf).* 2016;22:142-51.
- Shah A, Safaya A. Granulomatous slack skin disease: a review, in comparison with mycosis fungoides. *J Eur Acad Dermatol Venereol.* 2012;26:1472-8.
- Requena L, González-Guerra E, Angulo J, DeVore AE, Sanguenza OP. Anetodermic mycosis fungoides: a new clinicopathological variant of mycosis fungoides. *Br J Dermatol.* 2008;158:157-62.
- Lu YY, Wu CH, Lu CC, Hong CH. Hyperpigmentation as a peculiar presentation of mycosis fungoides. *An Bras Dermatol.* 2017;92:92-94.
- Schlichte MJ, Talpur R, Venkatarajan S, Curry JL, Nagarajan P, Duvic M. Verrucous presentation in patients with mycosis fungoides. *Int J Dermatol.* 2016;55:e126-9.
- Yamaguchi Y, Fujita Y, Hirata Y, Nishimura M, Shinkuma S, Natsuga K, et al. Psoriasiform mycosis fungoides masquerading as tumorous plaques. *Eur J Dermatol.* 2017;27:295-6.
- Azizpour A, Ghanadan A, Nasimi M, Etesami I. Psoriasiform mycosis fungoides: a rare form of the disease with review of the literature. *Dermatol Online J.* 2017;23:13030/qt9mv8rj7.
- Diakomopoulos A, Dalamaga M, Papadavid E. Understanding the enigmatic association between mycosis fungoides and psoriasis: report of two cases and review of the literature. *Metabol Open.* 2021;12:100148.
- Riyaz N, Sasidharanpillai S, Abdul Latheef EN, Davul H, Ashraf F. Pigmented purpuric dermatosis or mycosis fungoides: a diagnostic dilemma. *Indian Dermatol Online J.* 2016;7:183-5.
- Pousa CM, Nery NS, Mann D, Obadia DL, Alves Mde F. Granulomatous mycosis fungoides—a diagnostic challenge. *An Bras Dermatol.* 2015;90:554-6.
- Reggiani C, Massone C, Fink-Puches R, Cota C, Cerroni L. Interstitial mycosis fungoides: a clinicopathologic study of 21 patients. *Am J Surg Pathol.* 2016;40:1360-7.
- Pereira MAM, Toledo M, Arkader B, Pantaleao L. Interstitial mycosis fungoides. *J Bras de Patologia e Medicina Laboratorial.* 2021;57:e3312021.
- Wolf P, Cerroni L, Kerl H. Mycosis fungoides mimicking perioral dermatitis. *Clin Exp Dermatol.* 1992;17:132-4.
- Shapiro PE, LeBoit PE. Interstitial mycosis fungoides: setting the record straight. *Am J Surg Pathol.* 2017;41:282-3.
- Kadin ME, Hughey LC, Wood GS. Large-cell transformation of mycosis fungoides-differential diagnosis with implications for clinical management: a consensus statement of the US Cutaneous Lymphoma Consortium. *J Am Acad Dermatol.* 2014;70:374-6.
- Pulitzer M, Myskowski PL, Horwitz SM, Querfeld C, Connolly B, Li J, et al. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. *Pathology.* 2014;46:610-6.

Drug-induced lupus erythematosus

Lúpus eritematoso induzido por fármacos

Ana L. Gouveia¹ and Margarida Gonçalo^{1,2,a*}

¹Faculdade de Medicina, Universidade de Coimbra; ²Serviço de Dermatologia, Centro Hospitalar e Universitário de Coimbra. Coimbra, Portugal
^aORCID: 0000-0001-6842-1360

Abstract

Drug-induced lupus erythematosus is an autoimmune disease with unexpected onset after treatment with certain drugs. Clinically, this disease is very similar to idiopathic lupus erythematosus, although its manifestations are typically milder. In addition, the laboratory and histological changes of the induced forms are also not significantly different from the idiopathic condition, sometimes making the diagnosis of the drug-induced form a challenge for clinicians. This entity has been gaining relevance in the clinical setting and the number of drugs associated with it has been increasing, mainly due to the emergence of new biological therapies with a strong causal link with drug-induced lupus, such as tumor necrosis factor-alpha inhibitors. However, there are still no universally accepted diagnostic criteria to identify this disease, and information about its pathophysiology is still somewhat scarce, making it difficult to predict the most likely culprit drugs before there are enough reports to establish a strong link. In addition, although some risk factors have shown susceptibility for certain individuals, they are not yet fully understood. Given the possibility of disease reversal by the withdrawal of the offending drug, it is extremely important to be aware of the possible implication of a drug in the pathogenesis of this disease, and for clinicians who approach patients with lupus manifestations, particularly cutaneous manifestations, it is mandatory to look for the onset of new drugs used by the patient. This review will systematize the current knowledge about this drug-induced lupus, in terms of pathophysiology, clinical, histopathological, and laboratory manifestations, diagnosis, and treatment, as well as the most commonly implicated drugs.

Keywords: Drug-induced lupus erythematosus. Cutaneous lupus erythematosus. Subacute cutaneous lupus erythematosus. Chronic cutaneous lupus erythematosus. Anti-TNF α . COVID-19.

Resumo

O lúpus eritematoso induzido por fármacos (LEIF) é uma doença autoimune com aparecimento inesperado após o tratamento com determinados fármacos. Clinicamente, é muito semelhante ao lúpus eritematoso idiopático, ainda que as suas manifestações sejam tipicamente mais leves. Adicionalmente, as alterações laboratoriais e histológicas das formas induzidas também não são significativamente diferentes dos quadros idiopáticos, tornando, por vezes, o diagnóstico da forma induzida por fármacos um desafio para os clínicos. Esta entidade tem ganho cada vez mais relevância no contexto clínico e o número de fármacos associados tem vindo a aumentar, principalmente devido ao aparecimento de novas terapias biológicas com forte ligação causal com o lúpus induzido por fármacos, como os inibidores do fator de necrose tumoral alfa (anti-TNF α). Contudo, ainda não existem critérios de diagnóstico universalmente aceites para a identificação desta doença e a informação

*Correspondence:

Margarida Gonçalo
Email: mgoncalo@fmed.uc.pt

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acerca da sua patofisiologia ainda é algo escassa, o que torna difícil de prever os fármacos mais prováveis de a causar antes que haja número suficiente de relatos para estabelecer uma ligação. Além disso, apesar de já terem sido propostos alguns fatores de risco associados a uma maior suscetibilidade em alguns indivíduos, estes ainda não estão completamente esclarecidos. Face à possibilidade de reversão do quadro após a suspensão do fármaco, o alerta para o possível contributo de fármacos na patogenia de lúpus eritematoso é de extrema importância e deve estar presente no diagnóstico diferencial dos clínicos que abordam doentes com manifestações lúpicas, nomeadamente cutâneas, e que iniciaram novos fármacos. Nesta revisão far-se-á uma sistematização do conhecimento atual acerca do lúpus eritematoso induzido por fármacos, em termos de patofisiologia, manifestações clínicas, histopatológicas e laboratoriais, diagnóstico e tratamento, assim como os fármacos mais comumente implicados.

Palavras-chave: Lúpus eritematoso induzido por fármacos. Lúpus eritematoso cutâneo. Lúpus eritematoso cutâneo subagudo. Lúpus eritematoso cutâneo crónico. Anti-TNF α . COVID-19.

Introduction

Drug-induced lupus erythematosus (Di-LE) is an autoimmune phenomenon¹ that can affect the skin and/or multiple body systems, with a phenotype typically similar to idiopathic lupus erythematosus (LE). It occurs after chronic exposure to a particular drug (usually over months or years of use) and tends to resolve after drug discontinuation². This entity has been gaining more and more relevance in clinical practice, currently considered to represent approximately 15% of all causes of LE³.

As with idiopathic LE, Di-LE can be classified into drug-induced systemic LE (Di-SLE) and drug-induced cutaneous LE (Di-CLE), presenting either as the subacute or chronic subtype⁴. The differential diagnosis between drug-induced and idiopathic cases can be a challenge since clinical aspects, serology, and histopathology are identical⁵. However, they tend to differ in the extent to which they involve different organs and in their clinical course, since Di-LE usually presents as a milder clinical picture with fewer complications².

Drugs can either unmask clinically silent LE, induce LE exacerbations in a patient that has already been diagnosed (as reported with abatacept⁶), or trigger a “lupus-like” syndrome, which is the most frequent case².

There is difficulty in diagnosing this entity due to the lack of validated criteria, but it is important to draw attention to the relevance of timely identification of Di-LE and suspension of the culprit drug, which may allow disease remission. With a low awareness of this condition, the aim of this review is to systematize current knowledge about pathophysiology, clinical, and serological disease manifestations, with an update of associated drugs.

Epidemiology

Di-LE may account for approximately 15% of all LE cases³. It occurs mainly between 55 and 60 years of

age⁷, mostly in females and Caucasians⁸, but there are also rare pediatric cases reported in patients under treatment with infliximab, carbamazepine⁴, and valproic acid⁹.

Pathogenesis of drug-induced LE

The pathogenesis of Di-LE remains poorly understood. The fact that several drugs with distinct chemical structures and different pharmacological actions may be associated with Di-LE contributes to the hypothesis that multiple mechanisms are involved, and, in some cases, they may coexist². Genetic susceptibility, drug biotransformation, and epigenetic dysregulation, with changes in innate and adaptive immune response seem to be involved⁴.

Given the usual rapid clinical improvement after drug discontinuation, the autoimmune response in Di-LE can be considered as a transient change in immune response and not a significant affectation of the immune tolerance as in idiopathic LE². The risk of a drug to induce Di-LE increases with the number of changes that it causes in the individual's immunity. Procainamide and hydralazine, two of the drugs most frequently associated with Di-LE, induce changes both in the innate and adaptive immune response².

Genetic susceptibility

Genetic susceptibility is evident in Di-LE, but risk factors are different for each drug. Human leukocyte antigens (HLA) DR2, DR3, DR4², and HLA-B8³ have been associated with an increased risk for Di-LE induced by minocycline, terbinafine, and hydralazine². Hereditary complement deficiencies, namely, C4 null allele² and selective immunoglobulin A (IgA) deficiency, particularly with concomitant HLA-B8 and DR3

haplotypes, have also been hypothesized as risk factor for Di-LE¹⁰.

The slow acetylation phenotype may be a risk factor as some drugs inducing Di-LE, such as procainamide and hydralazine, are metabolized by acetylation through the enzyme N-acetyltransferase⁴ and, therefore, slow acetylators may accumulate more antibody-inducing metabolites².

A family history of SLE or Di-LE¹¹ or a personal history of another connective tissue disease¹² may also be considered a risk factor, as reported for terbinafine³.

Epigenetic dysregulation and autoreactivity/loss of tolerance

Biotransformed drugs and some of their metabolites are responsible for altering the epigenetic properties of B- and T-cells, leading to the formation of autoreactive cells that can induce Di-LE⁴.

Both hydralazine and procainamide inhibit DNA methylation in T-cells by decreasing the activity of DNA methyltransferase-1⁴ and hypomethylation of T-cell DNA which can alter gene expression profiles and, consequently, T-cell function⁸. This also results in increased expression of lymphocyte function-associated antigen 1 (LFA-1), leading to increased T-cell reactivity and loss of peripheral tolerance⁴, which may also occur in idiopathic SLE².

In addition, reactive metabolites of procainamide and hydralazine can interfere with central T-cell tolerance, leading to the production of autoreactive T-cells, with hydralazine leading B-cells to produce anti-histone antibodies (H2A-H2B-DNA)⁴.

Drug-induced alterations in innate and adaptive immunity

Drugs and/or their reactive metabolites can activate several pathways within the innate immune response and, therefore, enhance the presentation of self-peptides inducing autoimmunity or they can function as haptens and bind to macromolecules triggering an immune response with activation of autoreactive T and B lymphocytes, for example, by antigen mimicry⁴. Given the time lag between drug exposure and onset of clinical and serological abnormalities, the biotransformation of the drug into reactive metabolites is probably responsible for autoimmunity, rather than the drug itself¹.

Inhibition of the classical complement pathway can also contribute to the pathogenesis of the Di-LE, as in the case of hydralazine, penicillamine, isoniazid, and

metabolic products of procainamide⁴. These drugs can inhibit the covalent binding of complement factor C4 (classical pathway), increasing the concentration of circulating immune complexes by decreasing their clearance⁴.

Quinidine and procainamide inhibit the removal of apoptotic cells by macrophages which allow a greater number of self-antigens to remain longer in circulation and enhance autoantibody formation⁴.

Neutrophil extracellular traps (NETs), formed on neutrophil death/apoptosis and consisting of extrusion of a “network” of nuclear DNA and cytosolic proteins, have an important role in host defense, but increased NET formation (NETosis) and/or decreased NET clearance has been associated with different autoimmune diseases, including Di-LE². NETs function as a source of nuclear material rich in autoantigens and granule proteins that enhance the formation of autoantibodies or autoreactive T-cells⁴. In addition, they can cause direct toxicity in host tissues, especially in blood vessels².

Both hydralazine and procainamide promote NETosis, the first by increasing calcium influx and activation of peptidyl arginine-deiminase-4 that mediates chromatin decondensation¹³ and the latter by activating the muscarinic receptors of neutrophils⁴ and propylthiouracil increases the production and decreases the clearance of NETs². However, other Di-LE-inducing drugs such as minocycline and clozapine do not lead to NET formation².

Procainamide oxidation by activated neutrophils produces hydroxylamine (PAHA, a toxic metabolite) that combines with neutrophil myeloperoxidase (MPO) and creates cytotoxicity⁴ and hydralazine binds to MPO in intracytoplasmic neutrophil granules enhancing the release of cytotoxic and cell death products^{13,14}. This type of MPO-induced cytotoxicity enhanced by drug-causing LE *in vivo* is related to their ability to serve as a substrate for MPO *in vitro*⁷.

Type I interferons are involved in antiviral response and in bridging innate and adaptive immunity in normal individuals, but these type I interferons have been recognized as an important pathogenic factor in idiopathic SLE. They can be induced by viral particles or by DNA fragments, exposed namely after cell apoptosis or NETs¹⁵, and a chronic type I IFN production with a strong “type I IFN signature”, particularly in the skin, has emerged as a major marker in SLE and CLE¹⁶.

Reinforcing the role of type I interferons, there are reports of Di-LE in patients on treatment with IFN- α and IFN- α , but specially with IFN- α , estimated to occur in

0.15-0.7%¹⁷⁻¹⁹. These cases differ from Di-LE caused by other drugs as they lead to a higher frequency of anti-DNA antibodies (50%) and frequently have cutaneous involvement, also reinforcing the high involvement of type I IFN in CLE¹⁶.

Pathogenesis of Di-CLE

As for SLE, pathomechanisms involved in cutaneous disease are also multifactorial, but it is still uncertain whether similar pathways are responsible for cutaneous disease. The exception is the formation of NETs that are known to be involved in both conditions²⁰, and very probably inducing type I interferon, whose expression in the skin is one of the highest among all organs involved in idiopathic LE^{15,16}.

In some individuals, photosensitive drugs such as hydrochlorothiazide, terbinafine, and etanercept can trigger cutaneous LE in photoexposed areas⁷, particularly in patients who had already LE serological markers before drug exposure²¹. Apart from keratinocyte necrosis/apoptosis, photosensitive drugs increase Ro/SSA expression on the surface of keratinocytes, as in idiopathic subacute CLE, with consequent increased production of anti-Ro/SSA antibodies and cytotoxicity against these keratinocytes that express the Ro antigen on their surface²².

Chemotherapeutic agents may induce CLE through cell apoptosis, with release of nucleosides that will act as target for autoantigens and Type I -IFN production¹².

Clinical manifestations of drug-induced LE

The time from starting the drug to the onset of lupus manifestations varies widely between drugs, but Di-LE usually occurs after months to years of exposure². In the case of oncologic therapy, symptoms can occur within days of exposure⁷. The latency period may also be shorter (days or weeks) when the drug is reintroduced²³.

Compared to the idiopathic SLE, Guicciardi et al. reported that patients with Di-SLE are considerably older and have more systemic manifestations, which are probably related to the advanced age and use of more medication²⁴. Manifestations may affect many organs as in idiopathic SLE, but organ involvement is relatively specific to the offending drug⁸.

Constitutional symptoms such as fever, weight loss, anorexia, and fatigue¹ and symptoms such as arthralgia/

arthritis, myalgia, and serositis are the most frequent¹³. Cutaneous manifestations are less frequent, contrasting with 70% of skin involvement in idiopathic SLE^{25,26}. An exception is cases induced by anti-TNF α drugs where the skin is involved in > 80% of cases². Occasionally, sicca syndrome and Raynaud's phenomenon can also be found².

Central nervous system, renal, gastrointestinal, and hematological manifestations are rare³ and also less frequent than in idiopathic SLE², except for neurological involvement for quinidine (up to 30%)²⁷ and lupus nephritis-like syndromes induced by hydralazine²⁸⁻³⁰, sulfasalazine, penicillamine, anti-TNF α , propylthiouracil, apixaban^{31,32}, and also to phytotherapeutic agents³³ and anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis associated with hydralazine³⁰.

Di-CLE

Skin lesions in Di-CLE may present in an unspecified form or with the pattern of subacute or chronic CLE². Subacute CLE is the most common, accounting for 70-80% of cases⁷ and occurs mostly in older women often associated with photosensitivity⁷.

Cutaneous features are very similar to the idiopathic subacute CLE²⁴: erythematous, annular, papulosquamous lesions that do not usually evolve to scarring⁷ (Figs. 1 and 2), mainly on photoexposed areas, or occasionally in more protected areas³⁴. An atypical and more widespread lesion distribution³⁵, concomitant bullous and target lesions, vasculitis/purpura²², and erythema nodosum²⁶ should raise the suspicion of a drug-induced case, as well as a change in the phenotype of the disease⁵.

Chronic CLE is very rarely drug-induced⁷, corresponding to the least frequent subtype of Di-LE³⁴. It occurs mostly in women, around the age of 40 years³⁶, more often associated with 5-fluorouracil or anti-TNF α ⁷, tends to have a slower onset (months to years) and resolves over months³⁴. Lesions tend to occur more in photoexposed areas³⁴ and are clinically similar to the idiopathic form⁷ (Fig. 3).

Drug-induced lupus *tumidus* and *chilblain lupus* have also been described².

Histological characteristics

Differences between the histology of the idiopathic form of CLE and the drug-induced form have already been suggested, but studies are not concordant. Both forms are associated with focal vacuolization of the



Figure 1. Subacute cutaneous lupus erythematosus induced by isoniazid.



Figure 2. Subacute cutaneous lupus erythematosus induced by terbinafine in a patient with previous history of anti-Ro antibodies.

epidermal basal layer, perivascular and periadnexal lymphocytic infiltrates in the dermis, epidermal atrophy and edema, apoptotic keratinocytes and/or follicular obstruction²², and both can show granular IgM, IgG and C3 deposits at the dermoepidermal junction²².

Guicciardi et al. showed that subacute Di-CLE has no significant difference in the average number of eosinophils, basal layer cell liquefaction, keratinocyte necrosis, and depth and pattern of the inflammatory infiltrate but has less mucin deposition, more leukocytoclastic vasculitis, and IgM and C3 deposits in the basement membrane zone are less frequent²⁴, but for Hillesheim et al., mucin deposition is similar in both forms³⁷.



Figure 3. Hydrochlorothiazide-induced chronic cutaneous lupus erythematosus.

Laboratory findings

In Di-SLE erythrocyte, the sedimentation rate is high in up to 80% of patients⁸ whereas C-reactive protein tends to be normal, with the exception of quinidine-induced LE (high in 89% of cases)⁸. Anemia, leukopenia or thrombocytopenia are seldom found in Di-LE^{1,2}, except for thrombocytopenia reported in 47% of quinidine-induced LE⁸ and pancytopenia frequently associated with hydralazine³⁸. Coombs test is positive in < 30% and low complement levels are rare¹, except in some quinidine-induced forms (low C3 and/or C4 in up to 1/3 of cases)².

Autoantibodies to histone subunits, anti-histone antibodies (AHAs) are present in up to 95% of Di-SLE cases¹⁰ and are the hallmark and a very characteristic immunological marker of this form of Di-LE¹, particularly anti-H2A-H2B antibodies in contrast to anti-H3 and H4 histone subunits more frequent in the idiopathic forms². However, this differentiation is not commonly performed and also does not seem to add much

diagnostic value³⁹. AHAs can be IgG or IgM, although IgG is more prevalent in Di-LE³⁸. Still, their pattern depends on the culprit drug, with procainamide associated with both IgG and IgM and hydralazine and chlorpromazine predominantly IgM³⁸. Nevertheless, as AHAs are also present in > 50% of classic SLE, they cannot be used to distinguish drug-induced from idiopathic forms⁷. Furthermore, AHAs are not frequent in the cutaneous forms, and their presence is not synonymous with disease as they develop in 25% of patients treated with isoniazid, but only 1% of these develop clinical manifestations³⁹.

Antinuclear antibodies (ANAs) are frequent²; however, negative ANAs should not exclude the diagnosis, especially if the patient has other LE-associated autoantibodies²³. Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies have been identified, mainly in those induced by anti-TNF α agents¹. Anti-Smith (anti-Sm) antibodies are found in < 5% of Di-LE cases¹, but have recently been described in six cases of Di-SLE^{1,32,40-43}, one case of subacute Di-CLE⁴⁴, and one of chronic Di-CLE³⁶. Anti-phospholipid antibodies, such as lupus anticoagulant, have been found in a few cases¹³, but, in these cases, the drug may just be unmasking idiopathic SLE as in the case published by Sieiro Santos et al.⁴⁵. Anti-cardiolipin antibody has also been reported in association with hydralazine, procainamide and minocycline⁸, metimazole^{10,32,45}, apixaban^{10,32,45}, and infliximab^{10,32,45}.

ANCAs, both anti-proteinase-3 and anti-myeloperoxidase antibodies, have been identified in patients with minocycline and propylthiouracil-induced LE², especially in patients with renal and pulmonary vasculitis^{14,30,46}.

Anti-SSA/Ro (> 90%) and less frequently anti-SSB/La (< 50%) are similarly present in drug-induced and subacute CLE⁷, along with positive ANAs in 60-80% of cases⁴⁷ by seldom AHAs⁴⁸.

High autoantibody titers may persist for months to years after discontinuation of the offending drug, as opposed to clinical manifestations¹.

Diagnosis of Di-LE

Although this entity has been gaining relevance over the years, there is still no consensus about diagnostic criteria⁷ and a temporal link with clinical, pathological, and serological findings compatible with LE contributes to establishing the diagnosis⁴⁹. Borchers et al.⁸ have proposed the following criteria both for Di-SLE and Di-CLE: - continuous and sufficient exposure to a specific drug, - presence of at least one symptom consistent with

LE, - no history of disease before starting treatment, - temporal relationship between the start of the drug and onset of the manifestations, and - discontinuation of the drug and the disappearance of the manifestations¹. However, this definition still has some flaws, because there are reports of cases that persist despite drug discontinuation⁷ and cases of Di-LE in patients with a previous history of SLE⁵. Reappearance of drug reintroducing would contribute to the diagnosis, but this is not recommended³⁹.

Diagnosing Di-LE can be more difficult for larger latency periods, simultaneous introduction of several drugs, new therapies with little information about their long-term effects⁴, and for treatment of neoplastic or autoimmune diseases, as these underlying conditions may be confounding factors⁴⁹. In cases with several potentially suspected drugs, a probability algorithm such as Naranjo's can be used to guide which drug should be stopped first⁷.

Drugs frequently implicated in Di-LE

Over the years, an increasing number of drugs have been associated with Di-LE², particularly in recent years both due to new therapies used in oncology and autoimmune diseases² and due to new associations of "old" drugs⁷ (Table 1).

Drugs can be classified as high or low risk¹ or as high, medium, low, and very low risk of inducing SLE² (Table 2) or into definitely (isoniazid, procainamide, and hydralazine), probably (phenytoin and carbamazepine), possibly (lithium and lamotrigine) and recently reported to induce Di-LE^{4,50}. However, for instance, proton-pump inhibitors (PPIs) and terbinafine⁵¹ are not categorized.

Anti-TNF α -induced LE

LE induced by tumor necrosis factor-alpha inhibitors (anti-TNF α) is rare (< 1%), it affects mostly women^{45,52}, and in many cases, the drug just reveals a pre-existing LE². It is considered distinct, as it sets up several exceptions to the typical features of Di-LE, but the three main forms of LE have been described³⁶.

This seems to be a class effect but is particularly evident for infliximab⁴⁵ and etanercept⁵³. These drugs induce: - apoptosis enhancing formation of autoantibodies against nuclear antigens⁸; - negative regulation on C-reactive protein and TNF α with consequent decrease in the expression of the adhesion molecule CD44 and reduced clearance of apoptotic material⁸; - and increase in type I interferon levels, which influences plasma cell differentiation⁵¹ - "cytokine shift" with suppression of

Table 1. List of drugs more commonly associated with cutaneous lupus erythematosus, divided by subacute, chronic, and other types of CLE

Subacute cutaneous LE	Diuretics, hydrochlorothiazide ⁷ Diltiazem ² , amlodipine ³⁵ ACE inhibitors ⁴ , beta-blockers ⁷ , phenytoin, carbamazepine, lansoprazole, omeprazole, esomeprazole Anticholinergic agents: tiotropium ⁷ Terbinafine, antiretroviral therapy ⁴ Anti-TNF α , anti-IL17, anti-IL12/23 ⁷ Anti-PD1 (nivolumab, pembrolizumab)/anti-PDL1 (atezolizumab), anti-CTLA4 (ipilimumab) ⁷ , Immunoglobulins G, leflunomide ⁷ Mast cell inhibitors (mastinib), anti-CDK (palbociclib) ⁵¹ Allopurinol, mitotane, pirfenidone ⁴ Bupropion, ticlopidine, rosuvastatin, estroprogestatives ⁷ Paclitaxel, tamoxifen ⁵¹ , doxorubicin, docetaxel, gencitabine ⁷ , taxanes, pemetrexed, hydroxyurea ³⁴ , 5-FU compounds ⁶² , pazopanib, bevacizumab ²¹ Topical treatments: terbinafine, imiquimod cream ⁷ , topical beta-blocker ⁶³
Chronic cutaneous LE	Fluorouracil compounds ² , capecitabine, tegafur, and uracil/tegafur ⁶⁴ Non-steroidal anti-inflammatory drugs ⁷ , Anti-TNF α (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab ⁷), Antifungals, intravenous immunoglobulin ⁶⁵
Other forms of cutaneous LE	<i>Lupus tumidus</i> : ustekinumab, bortezomide ⁵⁸ "Chilblain lupus": infliximab, adalimumab, etanercept ⁵⁸ Rowell syndrome: terbinafine ⁷

LE: lupus erythematosus.

T-helper 1 and increase of T-helper 2 cells, with B-cell activation and autoantibody formation^{45,54}.

In TNF α -induced-LE cutaneous (Fig. 4), renal, cerebral, and hematological involvement is most commonly seen^{45,52} as well as other atypical manifestations such as hepatitis, pneumonitis, valvulitis, deep vein thrombosis, neuritis, and myositis have also been reported⁵².

ANAs and anti-dsDNA are very common (90% of cases)⁵⁵ as well as anti-cardiolipin antibodies (25% of cases)⁴⁵ but anti-histone antibodies are usually negative². Anti-dsDNA antibodies are predominantly IgM with less systemic pathogenicity than the IgG antibodies found in idiopathic SLE, and therefore, this anti-TNF α -induced LE is less severe⁵³. These autoantibodies are often present without clinically evident disease². Hypocomplementemia is relatively frequent².

In milder cases, patients can tolerate substitution to another anti-TNF α ^{25,54}, and some might tolerate treatment continuation, eventually adding immunosuppressive drugs⁴⁵.

**Figure 4.** Drug-induced SLE: erythematous asymptomatic lesions on malar areas in a patient who developed ANA after use of anti-TNF- α for Crohn's disease.

COVID-19 vaccine-induced LE

Given the need for rapid development of SARS-CoV-2 vaccines in response to the COVID-19 pandemic, there has not been sufficient time for studies about their adverse effects in the population and, recently, reports of vaccine-associated outbreaks of autoimmune diseases and vaccine-induced cases of LE have been reported⁴², as with previous vaccinations^{43,56}. Nevertheless, these effects should not discredit vaccination⁵⁶.

Patients with autoimmune diseases already have, *ad initium*, a higher propensity to develop complications from the vaccine. It has been reported that 1/3 of patients with idiopathic LE who received SARS-CoV-2 vaccination had an outbreak of their underlying autoimmune disease⁴³. Still, in addition to disease exacerbations, Sagy et al. reported the case of three patients with SLE onset after vaccination with the Pfizer BNT162b2 mRNA vaccine, two of whom developed cutaneous manifestations⁴³. Khanna et al. reported a case of SLE induced by the Pfizer BNT162b2 mRNA vaccine and reviewed eight other cases induced by the Pfizer, the Astra-Zeneca, and Moderna mRNA vaccines⁴². Most patients were female between 30 and 40 years old, and lupus involved the skin and the musculoskeletal system, followed by the renal and gastrointestinal systems⁴².

Possible mechanisms included molecular mimicry and the activation of toll-like receptors (TLRs) on antigen-presenting cells with production of specific autoantibodies⁴³ or activation of TLRs by the viral mRNA, in conjunction with cytosolic inflammatory components, namely, the pyrin domain of the NLR family (NLRP3), leading to the onset of inflammation and autoimmunity⁵⁶.

Table 2. Drugs associated with systemic lupus erythematosus, with organization according to the risk of inducing the systemic type

Very low risk	Statins, anti-TNF α ² Minocycline ⁴
Low risk	Carbamazepine, phenytoin, primidone, ethosuximide ¹ Penicillamine, methyldopa, sulfasalazine, minocycline, isoniazid, chlorpromazine, propylthiouracil ² Captopril, acebutolol ²⁶
Intermediate risk	Quinidine ² Isoniazid ⁴
High risk	Procainamide (20-30%) ⁴ Hydralazine (5-10%) ⁴

Reversibility and treatment of Di-LE

Clinical manifestations of Di-LE tend to resolve after drug discontinuation, the first recommended therapeutic step (2) that should be associated with lifestyle modifications such as smoking cessation and sun protection⁵¹.

If a lupus-like condition persists after drug withdrawal, treatment should be based on patient's manifestations², but this treatment can often be reduced or even discontinued as symptoms resolve⁵¹.

In skin lesions, topical agents, such as corticosteroids or calcineurin inhibitors, are recommended² or, when lesions are more generalized, systemic therapies such as anti-malarials, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids may be used². Systemic immunosuppressants such as azathioprine, cyclophosphamide, mycophenolate mofetil², or biologic therapeutics³ may be needed, particularly in Di-SLE with involvement of multiple organs and systems⁷.

Reintroduction of the culprit drug may be safe and effective in some cases with minor symptoms, but it is suggested that reintroduction should be associated with a short-term immunosuppressive treatment⁵⁷. Maintenance of treatment with the causative drug has been described in patients under therapy with some anti-TNF α (infliximab and adalimumab), in most cases associated with systemic immunosuppressive agents⁵⁸. This approach can be very useful, especially in patients with chemotherapy-induced LE³⁴.

For some therapeutic classes, such as PPIs, thiazide diuretics, anti-TNF α , and chemotherapy agents, class effects have been reported⁵⁹; thus, it may be necessary to contraindicate drugs of the same drug class⁷. There are also case reports of the disease recurrence after

switching pharmacological classes, which reinforces the idea that there may be some genetic susceptibility for Di-LE⁶⁰.

Resolution of clinical manifestations depends on several factors such as the type of drug, the type of clinical manifestations and their severity, and the characteristics of the patients, including their underlying disease². Serological findings take longer resolution⁶¹, so they should not be used for therapy adjustment and evaluation². When the manifestations are not reversible, it might mean that the condition originated from a pre-existing LE that was unmasked by a drug recently added to the patient's medication².

Regular follow-up after resolution and in regards to the suspicion of a possible genetic susceptibility for the development of autoimmunity is recommended¹³.

Conclusion

Di-LE is indeed gaining importance in current clinical practice and, consequently, the number of studies published on this topic has been increasing, as well as the knowledge about the disease and main culprit drugs. However, most publications are isolated clinical case reports, with few studies adding new information on more precise diagnostic criteria and better knowledge of pathophysiology, characteristics of the implicated drugs, and their risk factors. This might allow, in the future, to screen patients more likely to develop the disease and avoid higher-risk drugs in more susceptible patients. In addition, a greater understanding of Di-LE may also contribute to explain pathomechanisms involved in the idiopathic forms and help develop more targeted treatments.

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References

- Aly R, Zeng X, Upadhyay K. Drug-induced lupus secondary to ethosuximide in association with acute tubulointerstitial nephritis and nephrotic syndrome. *Pediatr Rep.* 2022;14:190-9.
- Vaglio A, Grayson PC, Fenaroli P, Gianfreda D, Boccaletti V, Giggeri GM, et al. Drug-induced lupus: traditional and new concepts. *Autoimmun Rev.* 2018;17:912-8.
- Hindosh N, Kotala R, Probasco L, Bal S. Terbinafine induced lupus erythematosus with progression to lupus nephritis. *Cureus.* 2022;14:e23887.
- He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. *Curr Opin Rheumatol.* 2018;30:490-7.
- Keyes E, Grinnell M, Vazquez T, Diaz D, Thomas P, Werth VP. Drug-induced subacute cutaneous lupus erythematosus in previously diagnosed systemic lupus erythematosus patients: a case series. *JAAD Case Rep.* 2021;12:18-21.
- Zamora EF, Callen JP, Schadt CR. Drug-induced subacute cutaneous lupus erythematosus associated with abatacept. *Lupus.* 2021;30:661-3.
- Bataille P, Chasset F, Monfort JB, De Risi-Pugliese T, Soria A, Francès C, et al. Cutaneous drug-induced lupus erythematosus: clinical and immunological characteristics and update on new associated drugs. *Ann Dermatol Venereol.* 2021;148:211-20.
- Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. *Ann N Y Acad Sci.* 2007;1108:166-82.
- Papadopoulou E, Saroglou M, Ismailos G, Fletsios D, Tsavlis D, Tryfon S. Pearls for the diagnosis and possible pathophysiological mechanisms of valproic acid-induced lupus erythematosus: a literature review. *Lupus.* 2022;31:650-8.
- Beernaert L, Vanderhulst J. Antithyroid drug-induced lupus erythematosus and immunoglobulin A deficiency. *Am J Case Rep.* 2020;21:e927929.
- Pérez-De-Lis M, Retamozo S, Flores-Chávez A, Kostov B, Pérez-Alvarez R, Brito-Zerón P, et al. Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). *Expert Opin Drug Saf.* 2017;16:1255-71.
- Cornacchia MA, Coromilas AJ, Gallitano SM, Frank RC, Halasz CL. Subacute cutaneous lupus erythematosus induced by gemcitabine in 2 patients with pancreatic cancer. *JAAD Case Rep.* 2019;5:596-601.
- Kirakossian D, Ghosh P. Drug-induced lupus, a one-time hit or a harbinger of future autoimmunity: a case report. *Perm J.* 2020;24:19.121.
- Espinosa MC, Ding B, Choi K, Cohen DN, Marcelli M, Hooze OW. A simultaneous presentation of drug-induced lupus with drug-induced ANCA vasculitis secondary to hydralazine use in a patient with sarcoidosis. *Proc (Bayl Univ Med Cent).* 2019;32:231-4.
- Ramaswamy M, Tummala R, Streicher K, da Costa AN, Brohawn PZ. The pathogenesis, molecular mechanisms, and therapeutic potential of the interferon pathway in systemic lupus erythematosus and other autoimmune diseases. *Int J Mol Sci.* 2021;22:11286.
- Merola JF, Wang W, Wager CG, Hamann S, Zhang X, Thai A, et al. RNA tape sampling in cutaneous lupus erythematosus discriminates affected from unaffected and healthy volunteer skin. *Lupus Sci Med.* 2021;8:e000428.
- Buchanan S, Rosemergy I, Healy P. Drug-induced subacute cutaneous lupus erythematosus due to treatment with interferon beta-1a. *N Z Med J.* 2013;126:98-101.
- Araujo-Fernandez S, Ahijon-Lana M, Isenberg DA. Drug-induced lupus: including anti-tumour necrosis factor and interferon induced. *Lupus.* 2014;23:545-53.
- Sladkova V, Mares J, Lubenova B, Hlustik P, Kanovsky P. Drug-induced systemic lupus erythematosus in interferon beta-1b therapy. *Neuro Endocrinol Lett.* 2011;32:4-6.
- Petty AJ, Floyd L, Henderson C, Nicholas MW. Cutaneous lupus erythematosus: progress and challenges. *Curr Allergy Asthma Rep.* 2020;20:12.
- Russell-Goldman E, Nazarian RM. Subacute cutaneous lupus erythematosus with positive anti-Ro antibodies following palbociclib and letrozole treatment: a case report and literature review. *J Cutan Pathol.* 2020;47:654-8.
- Gray T, Segars K, Farsi M, Ross R, Miller R. Drug-induced anti-Ro positive subacute cutaneous lupus in a man treated with olmesartan. *Dermatol Online J.* 2019;25:13030/qt3xf8k540.
- Rahman MF, Panezai MA, Szerlip HM. Hydralazine-induced pericardial effusion. *Proc (Bayl Univ Med Cent).* 2019;32:377-8.
- Guicciardi F, Atzori L, Marzano AV, Tavecchio S, Girolomoni G, Colato C, et al. Are there distinct clinical and pathological features distinguishing idiopathic from drug-induced subacute cutaneous lupus erythematosus? A European retrospective multicenter study. *J Am Acad Dermatol.* 2019;81:403-11.
- Barber C, Song EJ. New-onset systemic lupus erythematosus in a patient receiving risankizumab for psoriasis. *JAAD Case Rep.* 2022;25:104-6.
- McNamara K, Hughes OB, Strowd LC. Cutaneous drug eruptions including serum sickness-like reaction, symmetrical drug-related intertriginous and flexural exanthema, and drug-induced lupus. *Clin Dermatol.* 2020;38:641-7.
- Tayer-Shifman OE, Bingham KS, Touma Z. Neuropsychiatric systemic lupus erythematosus in older adults: diagnosis and management. *Drugs Aging.* 2022;39:129-42.
- Baradhi KM. An intriguing case of anemia and renal failure. *Proc (Bayl Univ Med Cent).* 2019;32:78-9.
- Khan N, Reichel R, Khurshid A, Tso K, Broussard J, Dass A. Hydralazine-induced isolated lupus nephritis. *Ochsner J.* 2020;20:187-92.
- Padala SA, Medepalli VM, Mohammed A, Nahman S. Hydralazine-induced dual antineutrophil cytoplasmic antibody positive vasculitis and nephritis. *Cureus.* 2020;12:e8911.
- Pan X, Yuan Y, Huang F, Tian M. Severe lupus induced by the tumor necrosis factor-alpha inhibitor Anbainuo: a case report. *J Int Med Res.* 2021;49:3000605211022510.
- Rakita U, Grushchak S, Guo L, Braniecki M, Mehta S. Atypical subacute cutaneous lupus in a patient on apixaban anticoagulation therapy: a case report and review of the literature. *Cureus.* 2021;13:e16571.
- Rashid AM, Ghani FA, Mat LN, Lim CT. Herbal medication triggering lupus nephritis-a case report. *BMC Complement Med Ther.* 2020;20:163.
- Sibaud V. Anticancer treatments and photosensitivity. *J Eur Acad Dermatol Venereol.* 2022;36(Suppl 6):51-8.
- Mizuta T, Kato M. Amlodipine-induced subacute cutaneous lupus erythematosus localized to non-sun-exposed areas. *Case Rep Dermatol.* 2021;14:71-6.
- Brehon A, Moguelet P, Guégan S, Abisror N, Barbaud A, Beal C, et al. Discoid drug-induced lupus erythematosus induced by antitumor necrosis factor agents is a very rare subtype of cutaneous lupus: three cases and literature review. *Dermatol Ther.* 2020;33:e13364.
- Hillesheim PB, Bahrami S, Jeffy BG, Callen JP. Tissue eosinophilia: not an indicator of drug-induced subacute cutaneous lupus erythematosus. *Arch Dermatol.* 2012 Feb;148(2):190-3. doi: 10.1001/archdermatol.2011.290. Epub 2011 Oct 17.
- Brar Y, Yang NR, Polyedath A. Hydralazine-induced lupus presenting with pancytopenia: a case report. *Cureus.* 2022;14:e29793.
- Lee AY. Clinical use of anti-histone antibodies in idiopathic and drug-induced lupus. *Immunol Med.* 2022;45:180-5.
- Cerqueira A, Seco T, Paiva D, Martins H, Cotter J. Isoniazid-induced lupus: when the cure can be lethal. *Cureus.* 2020;12:e7311.
- Selamet U, Hanna RM, Sisk A, Abdelnour L, Ghobry L, Kurtz I. Acute interstitial nephritis and drug-induced systemic lupus erythematosus due to chlorthalidone and amiodarone: a case report. *SAGE Open Med Case Rep.* 2020;8:2050313X20910029.
- Dempsey H, Aitchison G, Goble G, Snook R. Serologic presentation of lamotrigine-induced lupus. *Case Rep Neurol Med.* 2022;2022:8756308.
- Khanna U, Oprea Y, Mir A, Halverstam C. New diagnosis of systemic lupus erythematosus after COVID-19 vaccination: a case report and review of literature. *JAAD Case Rep.* 2022;30:30-4.
- Sagy I, Zeller L, Raviv Y, Porges T, Bieber A, Abu-Shakra M. New-onset systemic lupus erythematosus following BNT162b2 mRNA COVID-19 vaccine: a case series and literature review. *Rheumatol Int.* 2022;42:2261-6.
- Tarazi M, Aiempnakit K, Werth VP. Subacute cutaneous lupus erythematosus and systemic lupus erythematosus associated with abatacept. *JAAD Case Rep.* 2018;4:698-700.
- Santos CS, Castro CA, Morales CM, Álvarez ED. Anti-TNF- α -induced lupus syndrome: two case reports and review of current literature. *Z Rheumatol.* 2021;80:481-6.
- Rubin RL, Haluptzok RF, Davila LM. Severe hydralazine-induced lupus presenting as systemic lupus erythematosus. *Lupus.* 2020;29:509-13.
- Tierney E, Kirthi S, Ramsay B, Ahmad K. Ustekinumab-induced subacute cutaneous lupus. *JAAD Case Rep.* 2019;5:271-3.
- Di Bartolomeo L, Irrera N, Campo GM, Borgia F, Motolese A, Vaccaro F, et al. Drug-induced photosensitivity: clinical types of phototoxicity and photoallergy and pathogenetic mechanisms. *Front Allergy.* 2022;3:876695.
- Nogueira AR, Tabuas-Pereira M, Aragao A, Verissimo MT. A severe presentation of drug-induced lupus erythematosus. *J Med Cases.* 2019;10:246-8.

51. Jadhav P, Kulkarni T, Jadhav J, Desai S, Baviskar R. Levetiracetam-induced systemic lupus erythematosus. *J R Coll Physicians Edinb.* 2021;51:58-60.
52. Borucki R, Werth VP. Cutaneous lupus erythematosus induced by drugs-novel insights. *Expert Rev Clin Pharmacol.* 2020;13:35-42.
53. Shovman O, Tamar S, Amital H, Watad A, Shoenfeld Y. Diverse patterns of anti-TNF- α -induced lupus: case series and review of the literature. *Clin Rheumatol.* 2018;37:563-8.
54. Said JT, Elman SA, Merola JF. Evaluating safety and compatibility of anti-tumor necrosis factor therapy in patients with connective tissue disorders. *Ann Transl Med.* 2021;9:430.
55. Fonseca A, Sunny J, Felipez LM. Antitumor necrosis factor-alpha (TNF- α) infliximab-induced pleural effusion and pericarditis in crohn's disease. *Case Rep Pediatr.* 2021;2021:9989729.
56. Mantis J, Bhavsar R, Abrudescu A. Drug-induced lupus erythematosus associated with antiretroviral therapy in a patient with human immunodeficiency virus: a case report. *Cureus.* 2017;9:e1661.
56. Chen Y, Xu Z, Wang P, Li XM, Shuai ZW, Ye DQ, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. *Immunology.* 2022;165:386-401.
57. Pathak S, Cherry S, Samad S, Aftab A. Successful clozapine rechallenge in a patient with suspected drug induced lupus. *BMJ Case Rep.* 2019;12:e228574.
58. Shabeeb N, Hinshaw M, Pei S, Craddock L, Keenan T, Endo J. Clinical features of tumor necrosis factor- α -inhibitor induced chilblain lupus: a case series. *JAAD Case Rep.* 2021;12:81-4.
59. Ferro A, Filoni A, Pavan A, Pasello G, Guarneri V, Conte P, et al. Subacute cutaneous lupus erythematosus-like eruption induced by EGFR-tyrosine kinase inhibitor in EGFR-mutated non-small cell lung cancer: a case report. *Front Med (Lausanne).* 2021;8:570921.
60. Yoshikawa N, Matsubara E, Yamamoto M, Yamazaki H, Uehara M, Kamata M, et al. Drug-induced bullous pemphigoid and lupus erythematosus occurring under anti-TNF- α and IL-6 therapy in a patient with rheumatoid arthritis. *Intern Med.* 2020;59:2611-8.
61. Safadi MG, Smith K, Hassan S, Patel V, Viglione M, Zahner SL. Probable drug-induced lupus erythematosus by zonisamide. *JAAD Case Rep.* 2021;17:4-6.
62. Shakhbazova A, Marsch AF. Systemic 5-fluorouracil induced lupus erythematosus: a review of the literature. *Dermatol Online J.* 2019;25:13030/qt3nw0p7hn.
63. Bilewicz-Stebel M, Miziolek B, Bergler-Czop B, Stańkowska A. Drug-induced subacute cutaneous lupus erythematosus caused by a topical beta blocker-timolol. *Acta Dermatovenerol Croat.* 2018;26:44-7.
64. Cohen PR. Discoid lupus erythematosus lesions associated with systemic fluorouracil agents: a case report and review. *Cureus.* 2020;12:e7828.
65. Jennings T, Ahmed S, Aphale A, Lee J, Valdes-Rodriguez R. Intravenous immunoglobulin G use in patients with chronic inflammatory demyelinating polyneuropathy: an uncommon cause of drug-induced discoid lupus erythematosus. *Australas J Dermatol.* 2019;60:e208-10.

Keratosis lichenoides chronica: a diagnosis to remember

Queratose liquenóide crónica: um diagnóstico a lembrar

Ana S. Pereira^{a*}, José C. Cardoso, and Mariana Batista

Department of Dermatology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

^aORCID: 0000-0003-4930-4614

Abstract

Keratosis lichenoides chronica (KLC) or Nekam's disease, is an uncommon dermatosis, assumed for years as a variant of another inflammatory dermatosis (such as cutaneous lupus erythematosus or lichen planus) but currently accepted as a distinctive condition. Although pathophysiologic mechanisms need further research, clinical aspects of KLC are well-characterised, particularly lichenoid hyperkeratotic papules arranged linearly or in a reticulate pattern over the extremities, seborrheic-like dermatitis on the face and oral or genital erosions. Histopathology usually shows lichenoid interface dermatitis with numerous necrotic keratinocytes and parakeratosis. Keratosis lichenoides chronica (KLC) typically has a chronic progressive course with poor response to treatment. In the following case, we present a 56-year-old man with chronic dermatosis whose clinicopathological findings allowed the diagnosis of KLC. The patient was treated with acitretin, topical steroids and topical calcineurin inhibitors with partial improvement of the lesions.

Keywords: Interface dermatitis. Keratosis lichenoides chronica. Lichenoid eruptions. Nekam's disease.

Resumo

A Queratose liquenóide crónica (QLC) ou Doença de Nekam é uma dermatose pouco comum, entendida desde há anos como variante de outra dermatose inflamatória (como lúpus eritematoso cutâneo ou líquen plano), mas atualmente aceite como uma entidade distinta. Embora os seus mecanismos fisiopatológicos necessitem de mais investigação, os aspetos clínicos da QLC encontram-se bem caracterizados, particularmente pelas pápulas queratósicas liquenóides dispostas linearmente ou num padrão reticulado sobre as extremidades, dermatite seborreica facial e erosões orais ou genitais. A histopatologia demonstra geralmente uma dermatite de interface liquenóide associada a numerosos queratinócitos necróticos e cobertos por paraqueratose. A QLC tem tipicamente um curso progressivo crónico com resposta insatisfatória ao tratamento. No caso seguinte, apresentamos um homem de 56 anos de idade com uma dermatose crónica, cujos achados clinicopatológicos permitiram o diagnóstico de QLC. O doente foi tratado com acitretina, esteróides tópicos e inibidores de calcineurina tópicos com melhoria parcial das lesões.

Palavras-chave: Dermatite de interface. Doença de Nekam. Erupções liquenóides. Queratose liquenóide crónica.

*Correspondence:

Ana S. Pereira
E-mail: sfigpereira@gmail.com

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Introduction

Keratosis lichenoides chronica (KLC) is an uncommon mucocutaneous disorder originally described in 1895 by Kaposi, who called it 'lichen ruber acuminatus morbilliform'¹. Later, in 1938, Nekam took note of acrosyringeal hyperkeratosis in the case published by Kaposi and named the disease 'porokeratosis striata lichenoides' despite the lack of coronoid lamella². Finally, in 1972, Margolis et al. introduced the nomenclature currently used—'KLC'³.

Case description

A 56-year-old male, otherwise healthy, presented to the dermatology department with a 1-year history of persistent asymptomatic cutaneous lesions predominantly affecting the limbs and face. On examination, multiple keratotic violaceous papules and plaques were distributed over the dorsum of his hands and fingers (Fig. 1A), as well as on the medial aspect of both thighs, where they were arranged in a linear pattern (Fig. 1B). On his face, there were erythematous and squamous lesions located mainly in the midfacial area, resembling seborrheic dermatitis (Fig. 1C). Mucous membranes, genital region, scalp and nails were spared. The remaining physical examination was unremarkable and his routine blood tests, including viral serologies and autoimmunity markers, were normal.

There was no familiar history of similar complaints.

A skin biopsy performed on a thigh lesion revealed irregular acanthosis and hyperkeratosis with alternating areas of orthokeratosis and parakeratosis. In the upper dermis, there was a dense lichenoid infiltrate composed of lymphocytes and plasma cells, associated with multiple foci of vacuolar degeneration of the basal epidermal layer and apoptotic keratinocytes (Fig. 2).

This combination of clinical and histological findings strongly suggested the diagnosis of KLC. The patient declined to be tested for the nucleotide-binding domain and leucine-rich repeat-containing protein 1 (NLRP1) gene. Treatment was initiated with acitretin 35 mg daily, in addition to the topical application of tacrolimus 1% ointment on the face and clobetasol propionate ointment 0.05% on the extremities. At 6 months follow-up, the lesions on his hands had significantly improved. However, other lesions showed milder responses to the treatment.

Discussion

Keratosis lichenoides chronica (KLC), also known as Nekam's disease, is a rare dermatosis of uncertain

etiology. It appears most frequently in adults, with a peak of incidence in the 4th decade and slight predominance in males^{1,2,4}.

Previously perceived as the expression of other inflammatory conditions such as lichen planus, lupus erythematosus or lichen simplex chronicus^{5,6}, KLC is now considered a distinct entity since the detection of a gain-of-function mutation in the nucleotide-binding domain and leucine-rich repeat-containing proteins 1 (NLRP1) gene in a family with semi-dominantly inherited KLC⁷.

NLRP1 is an inflammasome sensor protein in high levels in keratinocytes and cutaneous fibroblasts. It is thought that the gain-of-function mutation in the NLRP1 gene causes constitutive inflammasome activation and leads to reactive keratinocyte proliferation^{7,8}. However, further studies are required to fully comprehend the pathogenesis of both familial and sporadic cases.

Clinically, KLC is characterised by lichenoid or keratotic violaceous papules arranged in a linear or reticulated pattern, especially on the limbs⁴. A seborrheic-like dermatitis eruption on the face is also a common finding of this disorder⁴. Less frequent features include oral and genital ulcerative lesions, palmoplantar keratoderma and onychodystrophy which are found, respectively, in 50, 40 and 30% of cases^{1,9,10}.

Regarding histology, typical findings are hyperkeratosis with focal parakeratosis, irregular acanthosis alternating with areas of atrophy, vacuolar degeneration of keratinocytes at dermoepidermal junction and chronic inflammatory infiltrate in the upper dermis consisting of lymphocytes, histiocytes and plasma cells (often around infundibula and acrosyringia)^{4,5}.

Several inflammatory dermatoses, such as lichen planus, lichen planus-psoriasis overlap, lichen planopilaris, pityriasis rubra pilaris and cutaneous lupus erythematosus may mimic KLC¹⁰.

Keratosis lichenoides chronica (KLC) has a chronic and progressive course and is highly resistant to therapy^{11,12}. The most effective treatment consists of oral retinoids at a dose of 0.3-0.6 mg/kg/day^{2,11}, although complete responses are infrequent¹¹. Phototherapy (psoralen plus ultraviolet A and narrow-band ultraviolet B) can be helpful, especially as an adjuvant treatment^{4,11}. Topical treatment, as well as systemic steroids, other immunosuppressants and antimalarials, are usually ineffective^{2,12}.

This case serves to highlight KLC as a well-defined disease with consistent clinical and histological characteristics. Its pathogenesis is still not fully understood, although recent progress has been made with the discovery of the possible contribution of the NLRP1 gene.



Figure 1. Clinical features. **A:** keratotic papules on the thighs, some arranged in a linear pattern; **B:** keratotic violaceous papules over the dorsum of the hand; **C:** facial seborrheic dermatitis-like eruption.

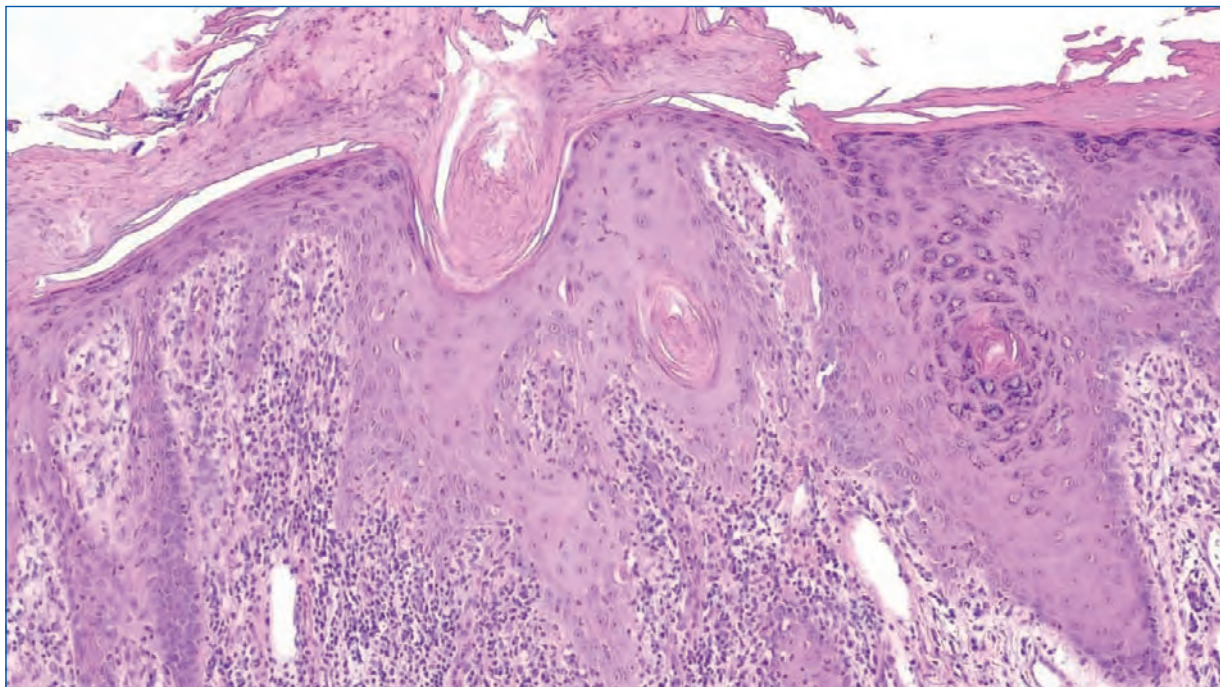


Figure 2. Histopathological aspects: irregular acanthosis with focal parakeratosis, apoptotic keratinocytes at various levels of the epidermis and mixed lichenoid infiltrate in the superficial dermis (H&E, 10x).

Despite its rarity, KLC is an entity that dermatologists should keep in mind, with the aim of detecting more cases and performing more investigations on both pathophysiology and therapeutical approaches.

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Conflicts of interest

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References

1. Wozniacka A, Schwartz RA, Omulecki A, Lesiak A, Sysa-Jedzejowska A. Keratosis lichenoides chronica a diagnostic and therapeutic challenge. *Clin Exp Dermatol*. 2006;31:48-50.
2. Martins L, Junior D, Almeida V, Horne M, Follador I. Keratosis lichenoides chronica - Case report. *An Bras Dermatol*. 2011;86:S148-51.
3. Margolis MH, Cooper GA, Johnson S. Keratosis lichenoides chronica. *Arch Dermatol*. 1972;105:739-43.
4. Aromolo IF, Giacalone S, Genovese G, Maronese CA, Marzano AV. Keratosis lichenoides chronica: a case report and focused overview of the literature. *Australas J Dermatol*. 2022;63:e99-2.
5. Boer A. Keratosis lichenoides chronica: proposal of a concept. *Am J Dermatopathol*. 2006;28:260-75.
6. Tchernev G, Nenoff P. Antigen mimicry followed by epitope spreading: a pathogenetic trigger for the clinical morphology of lichen planus and its transition to graham lassueur piccardi little syndrome and keratosis lichenoides chronica - medical hypotheses or reality? *An Bras Dermatol*. 2009;84:682-8.
7. Zhong FL, Mamai O, Sborgi L, Boussofara L, Hopkins R, Robinson K, et al. Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation *Cell*. 2016;67:187-202.e17.
8. Konstatinov KN, Søndergaard J, Izuno G, Obreshkova E. Keratosis lichenoides Chronica. *J Am Acad Dermatol*. 1998;38:306-9.
9. Demirci E, Boyvat A, Arica IE, Kocyigit P, Ozdemir E, Heper AO. Keratosis lichenoides chronica: marked response to PUVA in combination with acitretin. *Acta Derm Venereol*. 2005;85:552-3.
10. Aruna C, Ramamurthy D, Neelima T, Bandaru H. Nekam's disease. *Indian Dermatol Online J*. 2016;7:520-2.
11. Adışen E, Erdem O, Celepçi S, Gürer MA. Easy to diagnose, difficult to treat: keratosis lichenoides chronica. *Clin Exp Dermatol*. 2010;35:47-50.
12. Pistoni F, Peroni A, Colato C, Schena D, Girolomoni G. Keratosis lichenoides chronica: case-based review of treatment options. *J Dermatol Treat*. 2016;27:383-8.

Congenital cutaneous candidiasis in a term newborn

Candidíase cutânea congênita num recém-nascido de termo

Teresa Botelho^{1a*}, Inês Gameiro¹, Maria Relvas², João Teixeira², Mariana Batista², Ana Rodrigues-Silva¹, Patrícia Lapa¹, and Joaquim Tiago¹

¹Neonatology Service; ²Dermatovenereology Department. Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

^aORCID: 0000-0002-2884-9685

Abstract

Congenital cutaneous candidiasis (CCC) is a rare condition in neonates, mainly in term neonates, that develops in the 1st week of life. Its broad clinical spectrum makes it challenging to differentiate it from other exanthemas in the newborn. The involvement of palms and soles and the presence of pustules are important clinical clues for the differential diagnosis, with cultural examination confirming the diagnosis by identification of *Candida* spp. Treatment of clinically stable term neonates without evidence of invasive disease is currently controversial. We report a case of CCC in a term newborn with no evidence of invasive disease that evolved into a clinical cure after systemic and topical antifungal treatment.

Keywords: Congenital cutaneous candidiasis. Exanthema. Term newborn. Pediatric dermatology. Neonatal dermatology.

Resumo

A candidíase cutânea congênita é uma condição rara em recém-nascidos, principalmente em recém-nascidos de termo, que se desenvolve na primeira semana de vida e pode estar presente nas primeiras horas. Apresenta um amplo espectro de sintomas e pode ser difícil diferenciar de outros exantemas no recém-nascido. O envolvimento das palmas das mãos e plantas dos pés é uma característica importante no diagnóstico diferencial, e o exame cultural confirma o diagnóstico. O tratamento de recém-nascidos de termo clinicamente estáveis sem evidência de doença disseminada é controverso, e relatamos um caso de candidíase cutânea congênita extensa com resolução completa após tratamento sistêmico.

Palavras-chave: Candidíase cutânea congênita. Exantema. Recém-nascido termo. Dermatologia pediátrica. Dermatologia neonatal.

*Correspondence:

Teresa Botelho
E-mail: teresaabotelho@gmail.com

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Introduction

Congenital cutaneous candidiasis (CCC) is a rare condition in neonates. It is the result of a *Candida* spp. infection acquired in utero and is thought to occur via an ascending pathway from candida vulvovaginitis¹. One of the most accepted risk factors is the presence of an intrauterine foreign body (intrauterine device or cervical cerclage)². CCC can occur in infants regardless of the type of delivery, duration of rupture of membranes, or maternal diagnosis of candida vaginosis³. It is more common in preterm neonates under 27 weeks of gestational age, as well as in those with extremely low birth weight⁴. Immature, compromised mucocutaneous barriers and poor systemic host defences are thought to be predisposing factors in preterms. Extensive CCC in term neonates is rare, with only a few published reports in the literature.

Clinical case

A full-term (38 weeks) female infant was born by vaginal delivery with an appropriate birth weight for the gestational age (3044 gm). She was born to a healthy mother with a positive history of vaginal candidiasis before pregnancy. Serologies and prenatal ultrasounds were normal. There was no maternal history of herpes simplex infection, intrauterine device, cervical cerclage or amniocentesis. The mother tested positive for group B *Streptococcus* and received adequate antibiotic prophylaxis before delivery.

The Apgar score was 9/10/10 at 1, 5 and 10 minutes at birth. She had a regular clinical examination at birth.

At 24 hours of life, a few papules were noticed on the head and trunk, which rapidly and progressively worsened over the next 48 hours. On the third day, she developed a generalised papulopustular eruption involving the face, neck, trunk and extremities, including palms and soles, as well as diffuse bright erythema with erosions in the perineal area, multiple white plaques on the oral mucosa (Figs. 1 to 3), and purulent ocular exudate. There was no fever or other systemic symptoms. Based on clinical findings and skin examination, the diagnosis of CCC was strongly considered. Laboratory tests showed no evidence of systemic infection and a complete blood count revealed 18100/ μ L white blood cells (9500/ μ L neutrophils) and negative serum C-reactive protein concentration (0.03 mg/dL). Skin, ocular and blood cultures were collected. After multidisciplinary discussion, taking into consideration the extensive cutaneous and



Figure 1. Diffuse papulopustular eruption involving the entire integument.



Figure 2. Presence of papules and pustules on the palms.



Figure 3. A: oral mucosal and B: perineal area.



Figure 4. A and B: resolution with desquamation after therapy.

mucous membranes involvement, in the absence of systemic signs of infection, empiric treatment with intravenous fluconazole (12 mg/kg/day), oral nystatin and clotrimazole cream was started. Cerebrospinal fluid was not collected due to the lack of lesion-free

areas at the puncture sites. Considering CCC as the most likely diagnosis and the absence of clinical or laboratory evidence of systemic infection, no antibacterial nor antiviral therapy was added, pending clinical evolution and culture results. After a few days, the

culture of pustules and ocular exudate identified *Candida albicans* confirming the diagnosis. Blood cultures were negative. The mother's vaginal evaluation did not show any signs of active vulvovaginal candidiasis and vaginal swab cultures were negative.

Oral candidiasis resolved on the third day of treatment, and skin lesions progressively resolved with desquamation after fourteen days of intravenous fluconazole and topical clotrimazole (Fig. 4).

There was no evidence of immunodeficiency in the initial investigation, and the patient is currently under clinical follow-up.

Discussion

We present a case of extensive mucocutaneous candidiasis appearing in the first 48 hours of life. The involvement of the palms and soles, as well as the involvement of the oral mucosa and perineal region, were essential for suspecting the diagnosis. There was no evidence of invasive disease, and there was a good evolution under topical and intravenous antifungal agents.

Congenital cutaneous candidiasis (CCC) develops in the 1st week of life and may be present in the first few hours⁵. It presents a broad spectrum of symptoms, from rash to severe invasive disease. It is clinically characterised by a generalised exanthema, including erythematous macules and papules, vesicles and pustules that later undergo desquamation^{1,5}. The entire body can be affected, often involving the palms and soles, which is an essential feature for the differential diagnosis⁶. The most affected areas are usually the back, extensor surfaces and skin folds.

It is necessary to consider other differential diagnoses of exanthemas in newborns. Neonatal candidiasis differs from CCC by appearing after the first week of life and usually affects only the perianal region and oropharynx¹. Other differential diagnoses of CCC are extensive-erythema toxicum neonatorum, transient neonatal pustular melanosis, several infectious causes (group B *Streptococcus*, *L. monocytogenes*, herpes simplex virus, varicella zoster-virus, among others), miliaria or even Langerhans cell histiocytosis⁵. Some features help in the differential diagnosis—the presence of plaques in the umbilical cord (funisitis) should raise the suspicion of CCC but also of *L. monocytogenes* infection; lesions on the palms and soles are characteristic of *Candida* infection. Due to the difficulty in the differential diagnosis, it is imperative to confirm the diagnosis by cultural examination with isolation of *Candida* spp.

Usually, it is self-limiting but can progress to invasive diseases such as candidemia, pneumonia, arthritis and endocarditis⁴. The probability of invasive disease and

the mortality rate is inversely proportional to birth weight and gestational age.

Treatment of clinically stable term neonates without evidence of disseminated disease can be controversial. Nonetheless, studies also indicate that topical and shorter treatment cycles (< 14 days) are risk factors for the dissemination of *Candida* into the bloodstream³. In our case, due to the extensive mucocutaneous involvement with a higher risk of invasion, it was decided to initiate systemic therapy. Systemic treatment with fluconazole, amphotericin B deoxycholate and liposomal amphotericin B has been demonstrated to be effective³. In our hospital, amphotericin B deoxycholate is not available. Due to the low rate of fluconazole resistance in our unit and since liposomal amphotericin B is not the first choice in case of urinary tract infection⁷ (which could not be excluded due to the great mucocutaneous involvement contraindicating aseptic collection), it was decided to use fluconazole as first choice with excellent clinical outcome.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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References

1. Florens A, Maggolino G, Kamat M, Joseph T, Piette W, Pyati S. A full-term infant with rash at birth. *Pediatr Ann.* 2010;39:551-4.
2. Roqué H, Abdelhak Y, Young BK. Intra amniotic candidiasis. Case report and meta-analysis of 54 cases *J Perinat Med.* 1999;27:253-62.
3. Kaufman DA, Coggins SA, Zanelli SA, Weitkamp JH. Congenital cutaneous candidiasis: prompt systemic treatment is associated with improved outcomes in neonates. *Clin Infect Dis.* 2017;64:1387-95.
4. Aruna C, Seetharam K. Congenital candidiasis. *Indian Dermatol Online J.* 2014;5:44-7.
5. Darmstadt GL, Dinulos JG, Miller Z. Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. *Pediatrics.* 2000;105:438-44.
6. Rowen JL. Mucocutaneous candidiasis. *Semin Perinatol.* 2003;27:406-13.
7. Unni JC. Review of amphotericin B for invasive fungal infections in neonates and children. *Pediatr Infect Dis.* 2020;2:114-7.

Titanium hypersensitivity in a patient with a titanium medical implant

Hipersensibilidade ao titânio num doente com um implante médico de titânio

Ana G. Lopes^{a*}, Teresa Pereira, Maria J. Guimarães, Catarina Cerqueira, Joana Gomes, and Celeste Brito

Dermatology Department, Hospital of Braga, Braga, Portugal

^aORCID: 0000-0003-1103-1075

Abstract

A 53-year-old male patient with priors of psoriasis suffered a left tibial plateau fracture and underwent open reduction and internal fixation with a titanium plating system. He had no history of atopy or contact-hypersensitivity reactions to metals. Almost 1 year later, the patient continued to have chronic pain and edema at the site of the implant. On examination, the patient had a well-healed surgical incision on the left leg without erythema or induration but with tenderness to touch and two fluctuating nodular lesions. Subsequent allergy patch testing revealed an allergy-positive reaction to nickel sulfate, titanium oxalate and sodium tetrachloropalladate. The patient was diagnosed with titanium hypersensitivity secondary to recent implantation. The patient underwent hardware removal with a resolution of the complaints. The allergic risk of titanium material is smaller than that of other metal materials. Positive patch test reactions to titanium are rare and a negative patch does not exclude the diagnosis. Preimplant patients should be asked about a history of hypersensitivity reactions to metals and patch testing should be recommended for those who have experienced such reactions.

Keywords: Allergy. Medical implant. Patch testing. Titanium. Titanium hypersensitivity.

Resumo

Descreve-se o caso de um doente do sexo masculino de 53 anos, com antecedentes pessoais de psoríase, que sofreu uma fratura do prato tibial esquerdo, e foi submetido a uma redução aberta e fixação interna com um implante de titânio. O doente não referia história prévia de atopia ou reações de hipersensibilidade a metais.

Um ano após a cirurgia, o doente mantinha queixas de dor crónica e edema no local do implante. Ao exame dermatológico, era visível uma incisão cirúrgica linear bem cicatrizada na perna esquerda, sem eritema ou endurecimento, mas com aumento da sensibilidade ao toque e com 2 lesões nodulares móveis. Testes epicutâneos revelaram uma reação alérgica positiva ao sulfato de níquel, oxalato de titânio e tetracloropaladato de sódio. O doente foi diagnosticado com hipersensibilidade ao titânio secundário à recente colocação do implante de titânio na perna. O doente foi submetido a extração do material, com resolução das queixas. O risco de alergia ao titânio é mais pequeno do que com qualquer outro metal. Reações positivas nos testes epicutâneos são raras e um teste negativo não exclui o diagnóstico. Os doentes que vão ser submetidos a cirurgias

*Correspondence:

Ana G. Lopes

E-mail: ana.gabriela.castro@hb.min-saude.pt

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para colocação de implantes metálicos devem ser questionados acerca de história pessoal passada de reações de hipersensibilidade a metais e os testes epicutâneos pré-operatórios devem ser recomendados àqueles que têm estes antecedentes.

Palavras-chave: Alergia. Hipersensibilidade ao titânio. Implante médico. Testes epicutâneos. Titânio.

Introduction

Titanium has been considered to be a nonallergenic material, so it has been used in orthopaedic and spinal surgery, pacemakers, clips, coils and dental implants. Recent studies have reported rare cases of metal allergy caused by titanium-containing materials.

There are no standardized diagnostic tests and titanium allergy is often a diagnosis of exclusion.

We present a rare case of a confirmed metal allergy to a titanium plating system.

Case report

We describe the case of a 53-year-old male patient with priors of psoriasis, controlled with topical therapy. He had no history of atopy or contact reactions to metals.

The patient suffered a left tibial plateau fracture after a fall and underwent orthopedic surgery for open reduction and internal fixation with a titanium plating system. There were no complications during surgery or in the immediate postoperative period. The patient was discharged, with indications to complete a physiotherapy treatment plan which he began right away and completed after a few months, with regained mobility and muscle strength.

Almost 1 year later, the patient was referred to the dermatology department as he continued to complain of chronic pain and edema at the site of the implant on the left leg with two subcutaneous nodules that had developed 3 months after the surgery.

On dermatological examination, the patient had a linear surgical scar on the left leg without erythema or induration but with tenderness to touch and two fluctuating soft and elastic subcutaneous skin-colored nodules beneath the distal part of the scar. These nodules were mobile with the movements of the leg muscles (Fig. 1). There was no evidence of infection, loosening or failure of the metal plate.

In order to exclude a hypersensitivity reaction, patch testing was performed with the baseline series and an extended metal series (Chemotechnique diagnostics, Vellinge, Sweden). Readings were performed on the day (D) 3 and D7, according to European Society of Contact Dermatitis guidelines.

On D3, there were positive reactions to nickel sulfate 5% pet (++), titanium (IV) oxalate hydrate 5% pet (++), sodium tetrachloropalladate (II) hydrate 3% pet



Figure 1. Well-healed linear surgical incision on the left leg with two fluctuating subcutaneous nodular lesions beneath the distal part of the incision.

(+) and rhodium (III) chloride hydrate 2% pet (++). At D7 persisted the positive reactions to nickel sulfate 5% pet (++), titanium (IV) oxalate hydrate 5% pet (++) and sodium tetrachloropalladate (II) hydrate 3% pet (+), supporting the hypothesis of titanium hypersensitivity secondary to the recent implantation (Fig. 2-3).

The patient underwent removal of the titanium plating system on the left leg and 1 month after surgery, there was complete healing with no inflammatory signs, no pain or functional limitations, and the nodular lesions are no longer perceptible.

Discussion

Titanium is considered the most biocompatible metal due to its corrosion resistance, bio-inertness, osseointegration capacity and high fatigue limit. Therefore,



Figure 2. Result of patch testing at D7-allergy-positive reaction to nickel sulfate, titanium (IV) oxalate hydrate 5% and sodium tetrachloropalladate (II) hydrate.



Figure 3. Result of patch testing at D7-allergy-positive reaction to titanium (IV) oxalate hydrate 5% and sodium tetrachloropalladate (II) hydrate.

it is widely used in the medical field, such as plastic surgery, dental implants, pacemakers, neurosurgery and orthopedic surgery, significantly increasing exposure to this rare metal^{1,2}.

Despite its known biocompatibility, several studies have reported cases of suspected and confirmed allergic reactions to titanium salts, including two Portuguese case reports³⁻¹². Most are related to dental implant prostheses and screw fixation systems. One case occurred in a patient with allergic contact dermatitis who had dental implant prostheses and who exhibited allergic symptoms after orthopedic surgery².

In our case, the patient had no priors of atopy or contact reactions to metals and developed the symptoms after an orthopaedic surgery with the implantation of a titanium plating system.

Allergic reactions to titanium described in the literature are varied and include rash, urticaria, pruritus, oedema, eczematous lesions, hyperplastic lesions of soft tissue, impaired healing fractures, pain, and necrosis around the implants⁹. However, most instances of titanium allergy

appear as dermatitis around titanium products and symptoms resolve after the removal of the offending agent¹³.

In this case, the patient displayed pain, oedema and subcutaneous lesions on the site of the titanium implant, which raised the suspicion of titanium allergy.

Diagnosing titanium allergy is complicated because of the low sensitivity and specificity of the diagnostic tests available. The skin patch test has not yet been developed as the valid standardized test for titanium allergy and positive reactions to titanium have only rarely been demonstrated with skin testing¹⁴. The most widely used patch test preparation is titanium dioxide, but some studies suggest using other titanium salts as alternative reagents, such as 0.1 and 0.2% titanium sulfate in water solution or 0.1 and 0.2% titanium chloride pet¹⁵, 0.1% titanium tetrachloride² or titanium oxalate hydrate 5% pet, but it is yet to be confirmed which is the most adequate.

In this case, we used titanium oxalate hydrate 5% pet and obtained a positive test reaction at D3 that persisted at D7, ruling out irritation.

Before surgical implants, patients should be asked about a history of reactions to metals and patch testing should be recommended for those who have experienced such reactions.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Goutam M, Giriapura C, Mishra SK, Gupta S. Titanium allergy: a literature review. *Indian J Dermatol.* 2014;59(6):630.
2. Hosoki M, Nishigawa K, Miyamoto Y, Ohe G, Matsuka Y. Allergic contact dermatitis caused by titanium screws and dental implants. *J Prosthodont Res.* 2016;60(3):213-9.
3. Basketter DA, Whittle E, Monk B. Possible allergy to complex titanium salt. *Contact Dermatitis.* 2000;42:310-1.
4. Abdallah HI, Balsara RK, O'Riordan AC. Pacemaker contact sensitivity: Clinical recognition and management. *Ann Thorac Surg.* 1994;57:1017-8.
5. Hallab N, Merritt K, Jacobs J. Metal sensitivity in patients with orthopedic implants. *J Bone Joint Surg Am.* 2001;83:428-36.
6. Lhotka C, Szekeres T, Fritzer-Szekeres M, Schwarz G, Steffan I, Maschke M, et al. Are allergic reactions to skin clips associated with delayed wound healing? *Am J Surg.* 1998;176:320-3.
7. Tamai K, Mitsumori M, Fujishiro S, Kokubo M, Ooya N, Nagata Y, et al. A case of allergic reaction to surgical metal clips inserted for postoperative boost irradiation in a patient undergoing breast-conserving therapy. *Breast Cancer.* 2001;8:90-2.
8. Thomas P, Bandl WD, Maier S, Summer B, Przybilla B. Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: Case report and review of the literature. *Contact Dermatitis.* 2006;55:199-2.
9. Jain MS, Lingarajah S, Luvsannyam E, Somagutta MR, Jagani RP, Sanni J, Ebose E, Tiesenga FM, Jorge JM. Delayed Titanium Hypersensitivity and Retained Foreign Body Causing Late Abdominal Complications. *Case Rep Surg.* 2021 Mar 2;2021:5515401.
10. Dmochowski JM, Royal JT, Lourie GM. Could a Titanium Ulnar Shortening Plate Trigger a Metal Allergy? A Case Report. *J Wrist Surg.* 2019;8:503-7.
11. Matos AL, Pacheco V, Lopes R, Cardoso JC, Carvalho L, Rustemeyer T, et al. Inflammatory lung pseudotumor possibly related to titanium hypersensitivity. *Contact Dermatitis.* 2023.
12. Alves F, Ribeiro JC, Alves M, Gonalo M. Titanium allergy as a possible cause of extrusion of a bone conduction ear implant. *Contact Dermatitis.* 2020;83(2):148-9.
13. Egusa H, Ko N, Shimazu T, Yatani H. Suspected association of an allergic reaction with titanium dental implants: a clinical report. *J Prosthet Dent.* 2008;100:344-7.
14. Forte G, Petrucci F, Bocca B. Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention. *Inflamm Allergy.* 2008;7:1-18.
15. Okamura T, Morimoto M, Fukushima D, Yamane G. A skin patch test for the diagnosis of titanium allergy. *J Dent Res.* 1999;78:1135.

Cutaneous involvement by a mantle cell lymphoma

Envolvimento cutâneo por linfoma do manto

Ana G. Lopes^{1a*}, Teresa Pereira¹, André Coelho², Maria J. Guimarães¹, Catarina Cerqueira¹, Joana Gomes¹, and Celeste Brito¹

¹Department of Dermatology, Hospital de Braga; ²Department of Anatomical Pathology, Unilabs. Braga, Portugal

^aORCID: 0000-0003-1103-1075

Abstract

We describe the case of a 73-year-old female patient with priors of a mantle cell lymphoma (MCL), diagnosed 9 months ago, treated with chemotherapy, and currently with maintenance rituximab therapy, and a total knee replacement on the left leg 1 year ago. The patient presented to the Dermatology Department with patches on the left leg, with 3 months of evolution.

On examination, the patient presented infiltrated, confluent erythematous-violaceous patches and plaques, on the anterior surface of the left knee and leg, along the arthroplasty scar. No complaints associated. Blood work showed anaemia, neutropenia and an elevation of lactate dehydrogenase (LDH). A skin biopsy revealed occupation of the skin by a diffuse lymphoid proliferation, with intermediate-sized cells, with scarce cytoplasm, hyperchromatic nuclei and irregular borders. At immunohistochemistry, the cells were a cluster of differentiation (CD) 20+, CD5+, B-cell lymphoma 2 (Bcl-2) +, cyclin D1+ and CD3-. These findings are compatible with cutaneous involvement by MCL. The patient underwent radiotherapy on the left leg with regression of the lesions and is currently under chemotherapy. Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma (NHL). Cutaneous involvement is rare, secondary and means lymphoma dissemination. This case is also interesting for the site of skin involvement on a scar of knee replacement surgery.

Keywords: Cutaneous involvement. Cutaneous lymphoma. Lymphoma. Mantle cell lymphoma.

Resumo

Doente do sexo feminino, 73 anos, com antecedentes pessoais de linfoma do manto diagnosticado há 9 meses, para o qual fez quimioterapia, atualmente em tratamento de manutenção com rituximab, e artroplastia total do joelho esquerdo há um ano.

A doente vem à consulta de Dermatologia por manchas na perna esquerda com 3 meses de evolução. Ao exame dermatológico observavam-se manchas e placas eritematovioláceas, confluentes, infiltradas, na face anterior do joelho e perna esquerdas, ao longo da cicatriz de artroplastia. Sem queixas associadas. Sem lesões no restante tegumento cutâneo. Analiticamente apresentava anemia, neutropenia e aumento da LDH. A biópsia cutânea revelou pele ocupada por proliferação linfóide de padrão difuso, constituído por células de tamanho intermédio, escasso citoplasma, núcleo hipercromático e

*Correspondence:

Ana G. Lopes

E-mail: ana.gabriela.castro@hb.min-saude.pt

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contornos irregulares. Ao estudo imunohistoquímico as células eram CD20+, CD5+, BCL2+ e Ciclina D1+ Achados compatíveis com envolvimento cutâneo por linfoma do manto. A doente realizou radioterapia com regressão das lesões e encontra-se atualmente sob quimioterapia. O linfoma de células do manto é um linfoma não Hodgkin, de células B. O envolvimento cutâneo é raro, secundário e sinaliza disseminação da neoplasia. Este caso é interessante pelo local onde ocorreu o envolvimento cutâneo, na cicatriz de artroplastia do joelho.

Palavras-chave: Envolvimento cutâneo. Linfoma. Linfoma cutâneo. Linfoma do manto.

Introduction

Mantle cell lymphoma (MCL) is a B-cell NHL that develops from malignant B-lymphocytes within a region of the lymph node known as the mantle zone. MCL represents only 6% of all NHL¹.

Many affected individuals have widespread disease at diagnosis, with involved regions often including multiple lymph nodes, the spleen, and, potentially, the bone marrow, the liver and the gastrointestinal tract. Skin involvement is rare and is associated with progressive disease¹.

Our case report describes one of the rare cases of cutaneous involvement by an MCL.

Clinical significance

We describe the case of a 73-year-old female patient with priors of an MCL and a total left knee replacement 1 year ago.

Around 9 months ago, the patient started experiencing asthenia and undesired weight loss. Blood work showed anaemia and neutropenia, and clinical examination detected cervical lymphadenopathies. Biopsy of a lymph node diagnosed an MCL. Bone marrow biopsy showed involvement of the bone marrow and a positron emission tomography/computed tomography scan revealed multiple lymphadenopathies, thus an MCL stage IVB.

The patient underwent six cycles of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, with disease control, followed by maintenance rituximab therapy, currently on the second cycle.

The patient presented to the dermatology department with patches on the left leg, with 3 months of evolution.

On examination, the patient presented with infiltrated, confluent, shiny erythematous to violaceous patches and plaques on the anterior surface of the left knee and leg and on the arthroplasty scar (Fig. 1), with no associated complaints and no other relevant cutaneous lesions.

Blood work showed aggravation of anaemia, neutropenia and an elevation of LDH *de novo*.

A skin biopsy revealed dense occupation of the skin by a diffuse patterned lymphoid proliferation, with intermediate-sized cells, scarce cytoplasm, hyperchromatic nuclei and irregular borders (Figs. 2 and 3). In immunohistochemistry, the cells were positive for CD20, CD5, cyclin D1 and Bcl-2, and negative for CD3 and CD10 (Figs. 4 and 5). These findings are compatible with cutaneous involvement by MCL.

Maintenance therapy was stopped and the patient underwent radiotherapy on the left leg with regression of the lesions. The patient is currently under chemotherapy with R-BAC (rituximab, bendamustine, and cytarabine).

Discussion

Mantle cell lymphoma (MCL) is an uncommon form of NHL, accounting for 5–7% of all cases of NHL. It develops from malignant B-lymphocytes within a region of the lymph node known as the mantle zone¹. Around 90% of patients with MCL have a mutation that leads to the overproduction of a protein called cyclin D1 in the lymphoma cells².

It affects mostly men who are usually 60–70 years old¹.

The disease is typically widespread at diagnosis. Extranodal involvement, especially of the gastrointestinal tract, spleen and bone marrow, is fairly common in MCL³.

In the classification of World Health Organization, MCL is listed as an extracutaneous lymphoma secondarily involving the skin². Primary involvement of the skin with MCL is controversial and extremely rare. Secondary involvement is described to occur in 2% of all MCL cases and in 17% of cases with stage IV MCL, with about 30 cases reported⁴⁻⁶. This case was also a stage IV MCL.

Most cases report skin involvement of the trunk, followed by the face, upper limbs and less commonly, the lower limbs and abdomen. Also, the primary lesions are usually described as erythematous nodules but can also be papules and plaques^{2,4-6}. In this case, the patient presented with patches and plaques in only one lower limb at the site of a previous orthopaedic surgery which has never been described to our knowledge.

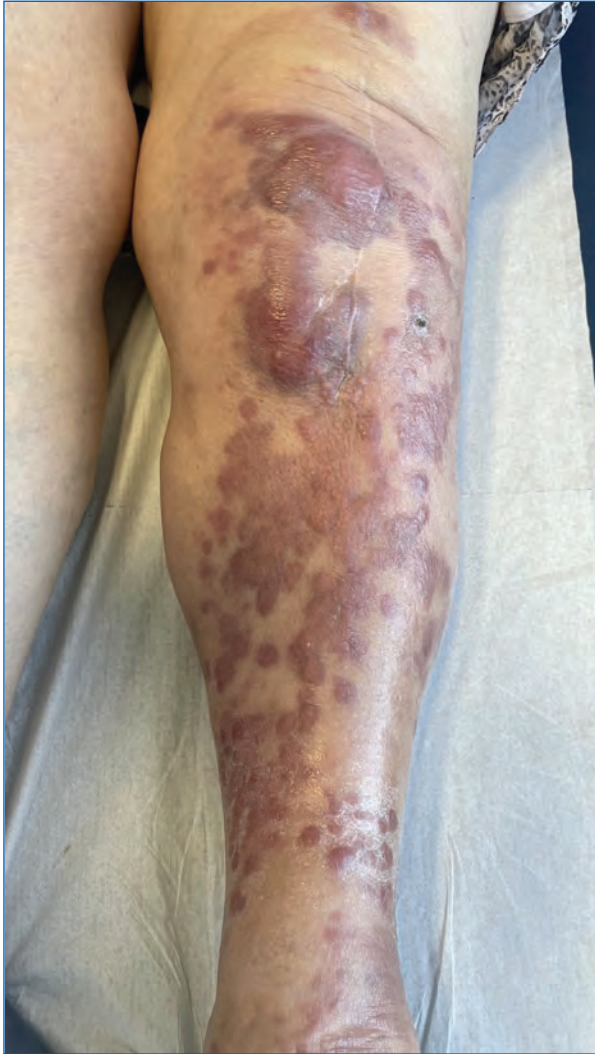


Figure 1. Erythematous-violaceous patches and plaques on the anterior surface of the left knee and leg.

The immunohistochemical profile of the MCL of our patient was comparable to that of published cases. According to the guidelines, the diagnosis of MCL should be established on the basis of morphological examination and immunophenotyping with the detection of cyclin D1 protein overexpression. Histologically MCL is composed of diffuse or nodular proliferations of B lymphocytes positive for B-cell markers, like CD79a, CD19, CD20, CD22 and CD5 and usually negative for CD10, CD23 and bcl-6⁶. In this case, the skin biopsy revealed a diffuse lymphoid proliferation with tumour cells positive for B-cell markers—CD20 and CD5, negative for CD3 and CD10 and overexpression of cyclin D1.

Patients who develop the cutaneous disease with widespread MCL typically have a progressive disease and, therefore, poor prognosis⁴.

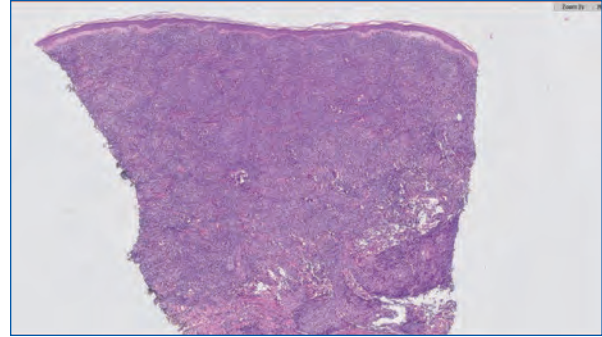


Figure 2. Skin biopsy with the dense occupation of the skin by a diffuse patterned lymphoid proliferation, sparing only a straight subepidermal band (grenz zone).

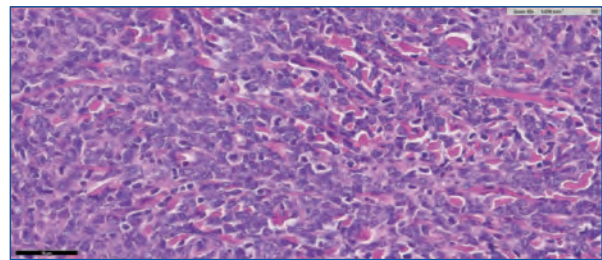


Figure 3. Lymphocytes with intermediate-sized cells, with scarce cytoplasm, hyperchromatic nuclei, and slightly irregular nuclear borders. Some mitotic figures can be seen.

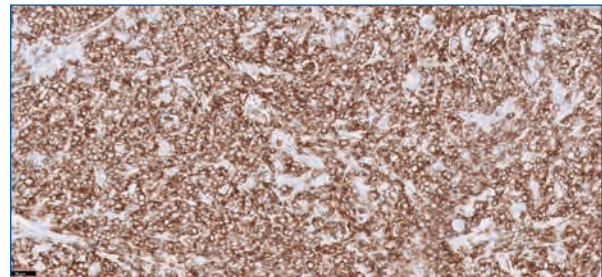


Figure 4. In immunohistochemistry, the cells were positive for CD20, therefore, from the B-lymphocyte lineage.

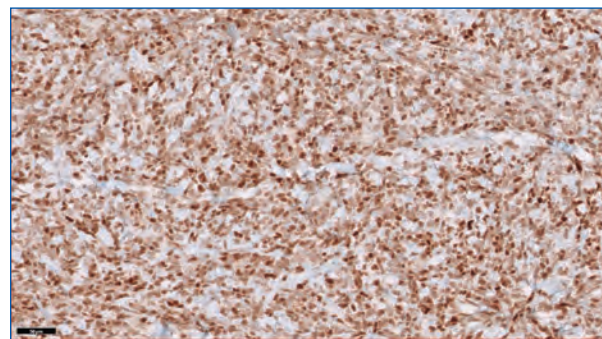


Figure 5. The cells are also positive for cyclin D1, a characteristic of MCL.

Although rare, skin involvement can be the first complaint of MCL in some cases and therefore, its first manifestation. Since this type of lymphoma is associated with a poor prognosis, a quick diagnosis and rapid treatment are crucial for survival.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Hrgovic I, Hartmann S, Steffen B, Vogl T, Kaufmann R, Meissner M. Cutaneous involvement as a rare first sign of systemic mantle cell lymphoma: a case report and review of the literature. *Mol Clin Oncol*. 2016;4:728-32.
2. Akay BN, Farabi B, Atak MF, Kuzu I, Heper AO. Cutaneous involvement of mantle cell lymphoma: report of two cases with dermatoscopic features. *Dermatol Pract Concept*. 2022;12:e2022064.
3. Lynch DT, Koya S, Acharya U, Kumar A. Mantle Cell Lymphoma. [Updated 2022 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK536985/>
4. Mazzuoccolo LD, Perez GA, Sorin I, Bravo AI. Primary cutaneous mantle cell lymphoma: a case report. *Case Rep Dermatol Med*. 2013;2013:394596.
5. Canpolat F, Taş E, Sönmez AA, Oktay M, Eskioğlu F, Alper M. Cutaneous presentation of mantle cell lymphoma. *Acta Derm Venereol*. 2010;90:548-50.
6. Kalińska-Bienias A, Ziarkiewicz-Wróblewska B, Kowalewski C, Woźniak K. Mantle cell lymphoma with skin involvement. *Postepy Dermatol Alergol*. 2015;32:229-34.
7. Gru AA, Hurley MY, Salavaggione AL, Brodell L, Sheinbein D, Anadkat M, et al. . Cutaneous mantle cell lymphoma: a clinicopathologic review of 10 cases. *J Cutan Pathol* 2016;43:1112-20.

Hand, foot, and mouth disease and palmoplantar erythrodysesthesia in a breast cancer patient: a challenging diagnosis

Doença mão-pé-boca e eritrodisestesia palmo-plantar em doente com neoplasia da mama

Dora Mancha^{1,a*}, Cláudia Brazão¹, Pedro Garrido¹, Luís Soares-de-Almeida^{1,2,3}, and Paulo Filipe^{1,2,3}

¹Dermatology Service, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte; ²Clínica Universitária de Dermatologia, Faculdade de Medicina da Universidade de Lisboa; ³Dermatology Research Unit, Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal
^aORCID: 0000-0002-6536-8936

Abstract

Cancer patients may experience several dermatological symptoms during treatment. We describe a case of synchronous presentation of hand, foot, and mouth disease (HFMD) and palmoplantar erythrodysesthesia (PPE) in a breast cancer patient. A 36-year-old female breast cancer patient under chemotherapy presented to our consult with a 1-week history of painful palmoplantar lesions associated with the recent onset of fever and dry cough. Her daughter had been diagnosed with HFMD. There was a positive immunoglobulin M (IgM) and IgG serology for coxsackievirus. We performed two skin biopsies; one specimen was consistent with HFMD, and the other one was with PPE. To the best of our knowledge, the synchronous presentation of HFMD and PPE has not yet been reported in the literature to date. PPE and immunosuppression might have been responsible for the atypical presentation and clinical severity of HFMD.

Keywords: Cancer. Coxsackievirus. Erythrodysesthesia. Immunosuppression. Palmoplantar. Neoplasm.

Resumo

O tratamento oncológico está associado a inúmeros efeitos adversos cutâneos—muitos deles já relatados na literatura. Descrevemos o caso de uma mulher com 36 anos, com antecedentes pessoais de neoplasia da mama, sob esquema de quimioterapia endovenosa, que recorreu à consulta por uma dermatose palmo-plantar dolorosa, associada a febre e tosse seca, com uma semana de evolução. Referia ter estado em casa a cuidar da filha de 18 meses, com o diagnóstico de doença mão-pé-boca (DMPB) há cerca de três dias. Analiticamente com leucopenia, PCR 12,2 mg/dL e serologia para *coxsackievirus* positiva (IgM, IgG). Foram realizadas duas biópsias cutâneas; uma amostra consistente com a DMPB e a outra com eritrodisestesia palmo-plantar (EPP). É o primeiro caso descrito na literatura de apresentação síncrona DMPB e EPP. A EPP associada à imunossupressão poderá ter sido responsável pela exacerbação da DMPB neste caso.

Palavras-chave: Câncer. Coxsackievirus. Eritrodisestesia. Imunossupressão. Palmoplantar. Neoplasia.

*Correspondence:

Dora Mancha
E-mail: dora.mancha@gmail.com

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Introduction

Breast cancer is the most frequently diagnosed cancer in women and ranks second among causes of cancer-related death. Cancer patients may experience several dermatological manifestations during treatment, including cutaneous adverse effects of chemotherapy^{1,2}. Moreover, in immunosuppressed patients, the most common infections are often associated with atypical clinical presentations.

Herein, we describe a case of synchronous presentation of HFMD and PPE in a breast cancer patient undergoing chemotherapy treatment.

Case presentation

A 36-year-old female patient presented to our outpatient dermatology department with a 1-week history of palmoplantar numbness and tingling associated with painful lesions on the palms and soles. She denied accompanying systemic symptoms. Her 18-month-old daughter had been diagnosed with HFMD 3 days before the beginning of cutaneous manifestations. Her medical history included breast cancer cT2N2M0. She was going through the third cycle of neoadjuvant chemotherapy with doxorubicin and cyclophosphamide. Examination revealed multiple erythematous purpuric papules, patches, vesicles and bullae on the palms and soles (Fig. 1). There were no mucosal lesions.

Two skin biopsies were performed, one on a palmar vesicle and the other on an erythematous papule on the arm. After a discussion with the oncology department, it was decided to delay the next chemotherapy cycle. Treatment consisted of betamethasone 1 mg/gm cream twice daily. After 1 week, there was a dissemination of the dermatosis associated with the recent onset of fever and dry cough. Laboratory studies revealed leucopenia $1.10 \times 10^9/L$ (normal range (NR) $4-11 \times 10^9/L$), neutropenia $0.24 \times 10^9/L$ (NR $1.9-7.5 \times 10^9/L$) and high C-reactive protein 12.2 mg/dL (NR < 0.5 mg/dL). There was a positive IgM and IgG serology for coxsackievirus.

The vesicle biopsy showed intraepidermal spongiosis, vesicle formation, epidermal necrosis and mixed inflammatory infiltrate, with eosinophils and lymphocytes, in the superficial dermis. These findings were consistent with HFMD (Fig. 2). Histopathological examination of the erythematous papule on the arm revealed orthokeratotic hyperkeratosis, atypical basal keratinocytes, oedema of the superficial dermis with a perivascular lymphocytic infiltrate and erythrocyte extravasation. These findings were compatible with PPE (Fig. 3).

Two weeks later, the dermatosis regressed, and blood work was normal. The patient went to the oncology consultation to schedule the next chemotherapy cycle. There was a clinical recurrence of mild PPE without the need to discontinue chemotherapy.

Discussion

Considering the clinical and epidemiological features described, the main differential diagnoses considered were HFMD, PPE, erythema multiforme (EM) and exanthem induced by other viruses. HFMD and PPE are mimickers of each other, and their diagnosis in this patient was only possible through histopathology.

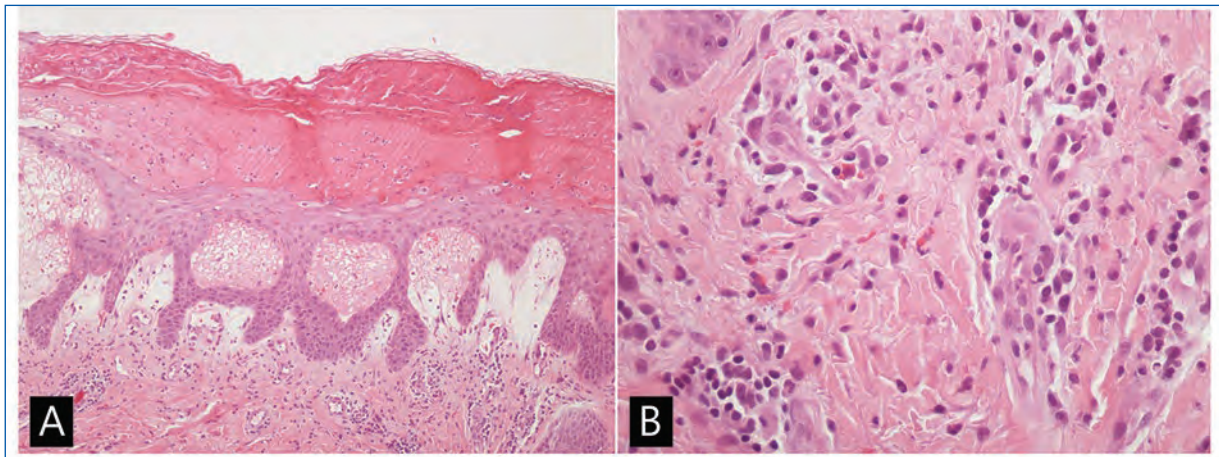
Hand, foot and mouth disease (HFMD) affects approximately 11% of exposed adults, but fewer than 1% of infected adults develop clinical manifestations³. Clinically, HFMD is characterized by fever, acral vesicular exanthema and painful stomatitis⁴. In our case, epidemiologic and clinical features led to the suspicion of HFMD. Progression with disseminated dermatosis was a concern in our patient due to her immunocompromised condition.

There is relatively limited histopathologic reporting on HFMD⁵. This likely reflects that HFMD in children is usually recognized by clinicians and does not typically require histopathology for diagnosis. In most cases reported in the literature, histopathological findings include spongiosis, extravasation of red blood cells and leukocytoclastic^{6,7}. In our case, a skin biopsy taken on a vesicle of the hand revealed features consistent with a viral infection, namely HFMD. Our case's main clinical differential diagnosis included EM and other viral infections. However, the absence of vacuolar alteration at the dermoepidermal junction and the presence of eosinophils in the inflammatory infiltrate make the EM hypothesis unlikely. On the contrary, the lack of classic viral cytopathic changes excludes a herpesvirus infection.

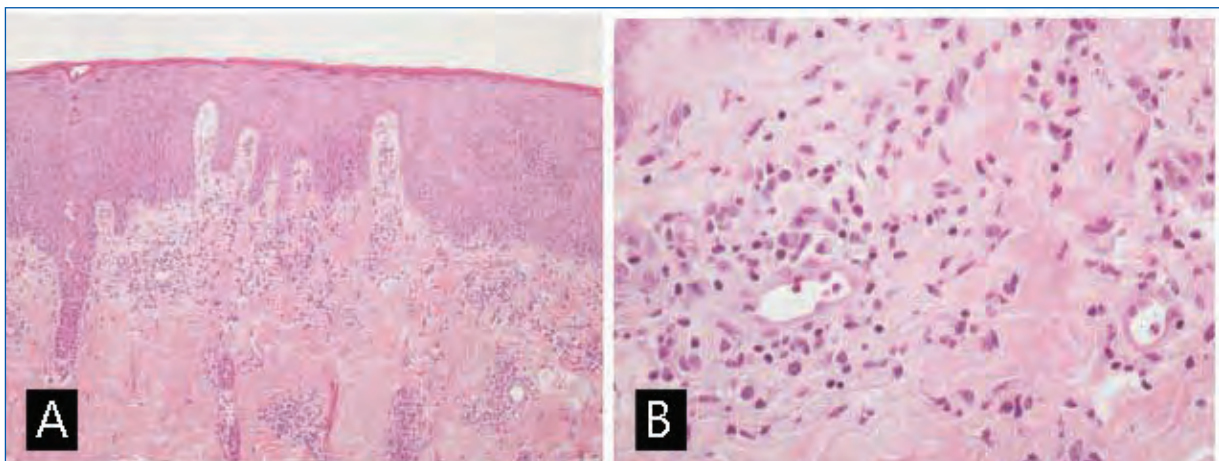
Palmoplantar erythrodysesthesia (PPE) is a toxic dermatologic reaction associated with specific chemotherapeutic agents, such as pegylated liposomal doxorubicin^{6,8,9}. We were concerned about the need for chemotherapeutic dose reductions or a switch to other drugs. The decision to delay the next chemotherapy cycle and the topical treatment ameliorated symptoms and helped to prevent the progression of both PPE and viral infection. Synchronous presentation of HFMD might have contributed to the worsening and possibly to overrating the PPE. The recurrence of mild PPE after resuming chemotherapy supports this observation. The histopathologic features in PPE most commonly described are dyskeratotic keratinocytes, basal



Figures 1A and B. Clinical picture—hand, foot and mouth disease & palmo-plantar erythrodysesthesia. **A:** erythematous purpuric papules and patches on the palms, **B:** erythematopurpuric papules, patches, vesicles and bullae on the soles.



Figures 2A and B. Hand, foot and mouth disease—skin biopsy. **A:** intraepidermal spongiosis, ballooning and reticular degeneration with intraepidermal vesicle formation and epidermal necrosis (H&E stain, magnification $\times 40$), **B:** inflammatory infiltrate with lymphocytes, eosinophils and neutrophils in the superficial dermis. Vascular dilatation and erythrocyte extravasation (H&E stain, magnification $\times 100$).



Figures 3A and B. Palmo-plantar erythrodysesthesia—skin biopsy. **A:** irregular acanthosis, orthokeratotic hyperkeratosis and dermal oedema (H&E stain, magnification $\times 40$), **B:** perivascular lymphocytic infiltrate and erythrocyte extravasation (H&E stain, magnification $\times 100$).

layer vacuolar degeneration, mild perivascular lymphocyte infiltrate, spongiosis, hyperkeratosis, and parakeratosis⁶. Our palmar papule biopsy revealed findings consistent with PPE.

To the best of our knowledge, the synchronous presentation of HFMD and PPE has not yet been reported in the literature. In our case, concomitant PPE and immunosuppression might have been responsible for the atypical presentation, longer course and clinical severity of HFMD.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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References

1. Gandhi M, Brieve JC, Lacouture ME. Dermatologic infections in cancer patients. *Cancer Treat Res*. 2014;161:299-7
2. Sanmartín O, Beato C, Suh-Oh HJ, Aragón I, España A, Majem M, et al. Clinical management of cutaneous adverse events in patients on chemotherapy: a national consensus statement by the Spanish Academy of Dermatology and Venereology and the Spanish Society of Medical Oncology. *Actas Dermosifiliogr (Engl Ed)*. 2019;110:448-9
3. Ramirez-Fort MK, Downing C, Doan HQ, Benoist F, Oberste MS, Khan F, et al. Coxsackievirus A6 associated hand, foot and mouth disease in adults: clinical presentation and review of the literature. *J Clin Virol*. 2014;60:381-6
4. Bian L, Gao F, Mao Q, Sun S, Wu X, Liu S, et al. Hand, foot, and mouth disease associated with coxsackievirus A10: more serious than it seems. *Expert Rev Anti Infect Ther*. 2019;17:233-2
5. Laga AC, Shroba SM, Hanna J. Atypical hand, foot and mouth disease in adults associated with coxsackievirus A6: a clinico-pathologic study. *J Cutan Pathol*. 2016;43:940-5
6. Lorusso D, Di Stefano A, Carone V, Fagotti A, Pisconti S, Scambia G. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). *Ann Oncol*. 2007;18:1159-4
7. Second J, Velter C, Calès S, Truchetet F, Lipsker D, Cribier B. Clinico-pathologic analysis of atypical hand, foot, and mouth disease in adult patients. *J Am Acad Dermatol*. 2017;76:722-9
8. Kwakman JJM, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy-induced hand-foot syndrome. *Oncol Rev*. 2020;14:442
9. Nagore E, Insa A, Sanmartín O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome. Incidence, recognition and management. *Am J Clin Dermatol*. 2000;1:225-4

Giant BCC of the scalp after telmisartan/amlodipine: potential role of nitrosamine contamination as main cause for skin cancer development

CBC gigante do couro cabeludo após telmisartana/amlodipina: papel potencial da contaminação por nitrosamina como principal causa para o desenvolvimento de câncer de pele

Georgi Tchernev^{1,2,a} and Simona Kordeva^{1,b*}

¹Onkoderma-Clinic for Dermatology, Venereology and Dermatologic Surgery; ²Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, Sofia, Bulgaria

ORCID: ^a0000-0002-0365-3504; ^b0000-0002-1768-8601

Abstract

The problem of drug-induced cancers, and in particular skin cancers after intake of various antihypertensive drugs, is increasing, but at the same time is gaining some clarity. In addition to melanocytic cancers, development of keratinocytic cancers is increased after the administration of sartans. It is believed that the procarcinogenic potential of the medication could be due to contamination of tablets with nitrosamines, which are known as mutagens. Regardless of the presence of angiotensin receptors in the skin and tumor tissue, the pharmacologic influence of the sartan is considered to be secondary and insignificant in relation to the processes of carcinogenesis. In certain cases, this influence is even defined as an antitumorous effect. We present a female patient who had been taking telmisartan/amlodipine 80/5 mg daily for 9 years and, after 4-5 years, developed a scalp tumor, confirmed histopathologically as a basal cell carcinoma (BCC) and treated successfully by surgical excision. The discussion is mainly focused on the potential role of nitrosamines as a new key player in the pathogenesis of keratinocytic cancers and BCC in particular.

Keywords: Nitrosamines. Basal cell carcinoma. Keratinocytic cancer. Dermatologic surgery. Telmisartan. Amlodipine.

Resumo

O problema dos cânceres induzidos por drogas, e em particular os cânceres de pele após a ingestão de vários medicamentos anti-hipertensivos, está aumentando, mas ao mesmo tempo está ganhando alguma clareza. Além dos cânceres melanocíticos, o desenvolvimento de cânceres queratinocíticos aumenta após a administração de sartans. Acredita-se que o potencial procarcinogênico do medicamento possa ser devido à contaminação dos comprimidos com nitrosaminas, conhecidas como mutagênicas. Independentemente da presença de receptores de angiotensina na pele e no tecido tumoral, a influência farmacológica do sartan é considerada secundária e insignificante em relação aos processos de carcinogênese. Em certos casos, essa influência é até definida como um efeito antitumoral. Apresentamos uma paciente que fazia uso diário de

*Correspondence:

Simona Kordeva

E-mail: simonakordeva97@gmail.com

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telmisartan/amlodipina 80/5 mg por 9 anos e após 4-5 anos desenvolveu um tumor no couro cabeludo, confirmado histopatologicamente como um carcinoma basocelular (CBC) e tratado com sucesso por excisão cirúrgica. A discussão está focada principalmente no papel potencial das nitrosaminas como um novo ator-chave na patogênese dos cânceres queratinocíticos e do CBC em particular.

Palavras-chave: Nitrosaminas. Basalioma cancro cutâneo. Tumor queratinocítico. Cirurgia dermatológica. Telmisartan. Amlodipina.

Introduction

Systemic treatments with sartans, and in particular telmisartan, are generally associated with a more frequent association with all forms of human cancer¹. According to other scientific works, this risk is determined by the total cumulative intake of sartans over a certain period of time².

Literature data has linked both keratinocytic and melanocytic cancers to the use of sartans³.

The simultaneous occurrence of basal cell carcinomas (BCC) and dysplastic nevi after taking sartans or sartans in combination with hydrochlorothiazide could be considered extremely important, eventually confirmatory, regarding the thesis that potential contamination with nitrosamines is able to generate multiple forms of cancer or skin cancer and/or its precursors^{4,5}. Contamination with mutagenic nitrosamine remains the link between the intake of sartans and the development of skin cancer. The recently confirmed presence of nitrosamines in hydrochlorothiazide (within monomedication or in combination), could reinforce the mentioned assumptions⁶.

Case report

A 69-year-old female came to the dermatology department with a 5-year-old tumor formation on the scalp in close proximity to the frontal region, that had been growing for about five years prior to the consultation. Physical examination showed a giant tumor, 5-7 cm in diameter, covered with hemorrhagic crusts, with undefined borders (Fig. 1A). A biopsy taken pre-operatively confirmed the histopathological diagnosis of basal cell carcinoma.

Due to comorbidities (arterial hypertension known for 13 years, hypertriglyceridemia, hypercholesterolemia and sinus tachycardia) the patient was under systemic therapy with Telmisartan 80 mg/Amlodipine 5 mg once daily for 9 years, Hydroxyzine 25 mg once daily in the evening and Chlorthalidone 25 mg once daily for 2 years. Glucose level was 7.15 mmol/L (normal range 3.9-5.6 mmol/L), but other blood tests were normal. A

Computerized Tomography of the head showed a normal brain image without deviations or changes in the bone structure of the frontal bone.

After consultation with a cardiologist, the medication was switched to moxonidine 0.2 mg twice daily, Nebivolol 2.5 mg once daily, and clonidine when needed.

The tumor was excised under general anesthesia followed by reconstruction with an advancement rotation flap. Histopathology showed a stage 2 (T2N0M0) nodular type of basal cell carcinoma without evidence of metastases. There was a good cosmetic result, and outpatient follow-up showed no tumor recurrence (Fig. 1B,C).

Discussion

Nitrosamines are well-known mutagens, carcinogens that without any doubt are causing in vivo different types of carcinomas such as: cancers of the bladder, lung, stomach, leukaemia, multiple myeloma, oesophagus, prostate, pancreas and liver⁷. Their pathogenetic role in the development of almost all forms of cancer remains undeniable and well-defined^{1,2,7}, either after inhalation⁸ or oral intake should. Their procarcinogenic effect remains statistically significant after taking sartans potentially contaminated with nitrosamines, especially for keratinocyte cancer, confirmed in serious retrospective analyses: unadjusted OR (95% CI) for BCC: 2.16 (1.85-2.82), as well as adjusted OR (95% CI) for BCC: 2.86 (2.13-3.83)⁸.

A two-fold increased expression of the Angiotensinogen gene in tumor cells of patients with BCC has been shown⁹. Although the role of the reninangiotensin system in the skin physiology is undeniable¹⁰, it remains unclear whether this expression is a result or a cause for the development of BCC.

A number of publications have established a link between sartans administration and the increased risk for melanoma progression in the experimental environment^{11,12}. An interesting recent publication indicated that valsartan contaminated with nitrosamines was associated with a 10% higher risk of developing melanomas¹³. Regarding BCC, such observations are



Figure 1. A-C: giant tumor formation of the scalp, 5/7 cm in size, covered with hemorrhagic crusts, with undefined borders (a). Outpatient follow-up with primarily healing wound and good aesthetic outcome (b,c).

completely absent, but the present case will perhaps be accompanied by other reports in the future. Currently, sartan use is associated with a significantly increased risk of actinic keratoses development, which are perceived as preforms of keratinocyte cancer¹⁴.

According to expert conclusions of specialised collectives, which are focused on monitoring the possible side effects of nitrosamines, their potential availability in sartans, ACE inhibitors, thiazide diuretics, metformin, and ranitidine, could lead to skin cancer development¹⁵.

The potential role of nitrosamines is mentioned within the perspective of large-scaled retrospective analyses⁸. According to them, both sartans and thiazide diuretics, but also ACE inhibitors, are associated with an over two-fold to nearly three-fold increased risk of developing BCC⁸. Batches of all these three classes of medications have been withdrawn from distribution in recent years due to the elevated concentrations of nitrosamines, many times exceeding the so-called ADIs (Acceptable daily intake doses).

Following statistical results and analyses⁸, it remains unlikely that the link between the three types of skin cancers (BCCs, Squamous cell carcinomas and melanomas) and different classes of antihypertensive medication with distinct pharmacologic activities is sporadic, but very probably related to common nitrosamine contamination of all these classes of drugs⁸.

In this case report, the absence of painful sunburns in the patient's history, as well as the long-term use of telmisartan (potentially contaminated with nitrosamines), reinforce this pathogenetic relationship.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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References

1. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol*. 2010 Jul;11(7):627-36. doi: 10.1016/S1470-2045(10)70106-6. Epub 2010 Jun 11. PMID: 20542468; PMCID: PMC4070221.
2. Sipahi I. Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: Meta-regression analysis of randomized trials. *PLoS One*. 2022 Mar 2;17(3):e0263461. doi: 10.1371/journal.pone.0263461. PMID: 35235571; PMCID: PMC8890666.
3. Tchernev G, Poterov G, Patterson JW, Malev V. Multiple verrucous carcinomas and giant acral melanoma developing after antihypertensive therapy with valsartan and olmesartan. *J Medical Review (Bulgarian)* 2020; 56(5):58-60.
4. Malev V, Tchernev G. Dysplastic nevus and BCC development after antihypertensive therapy with Valsartan and Hydrochlorothiazide!? *Clin Res Dermatol Open Access* 2019;6(5):1-2.
5. Tchernev G, Oliveira N, Kandathil LG, Patterson JW. Valsartan (or/and Nitrosamine) induced BCC and dysplastic nevi: current insights. *Clin Res Dermatol Open Access* 2021;8(4):1-6.
6. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accuretic>
7. Hidajat M, McElvenny DM, Ritchie P, Darnton A, Mueller W, van Tongeren M, Agius RM, Cherrie JW, de Vocht F. Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. *Occup Environ Med*. 2019 Apr;76(4):250-258. doi: 10.1136/oemed-2018-105181. Epub 2019 Feb 16. PMID: 30772818; PMCID: PMC6581114.

8. Nardone B, Majewski S, Kim AS, Kiguradze T, Martinez-Escala EM, Friedland R, Amin A, Laumann AE, Edwards BJ, Rademaker AW, Martini MC, West DP. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. *Drug Saf.* 2017 Mar;40(3):249-255. doi: 10.1007/s40264-016-0487-9. PMID: 27943160.
9. Papaggeorgopoulos J, Angelopoulou A, Avgoustidis D, Koronellos N, Derka S, Vassiliou S, Yapijakis C. Association of Polymorphisms in the Genes of Angiotensinogen and Angiotensin Receptors With Risk for Basal Cell Carcinoma. *Anticancer Res.* 2019 Oct;39(10):5525-5530. doi: 10.21873/anticancer.13745. PMID: 31570446.
10. Silva IMS, Assersen KB, Willadsen NN, Jepsen J, Artuc M, Steckelings UM. The role of the renin-angiotensin system in skin physiology and pathophysiology. *Exp Dermatol.* 2020 Sep;29(9):891-901. doi: 10.1111/exd.14159. PMID: 32697884.
11. Olschewski DN, Hofschroer V, Nielsen N, Seidler DG, Schwab A, Stock C. The Angiotensin II Type 1 Receptor Antagonist Losartan Affects NHE1-Dependent Melanoma cell Behavior. *Cell Physiol Biochem.* 2018;45 (6):2560–2576. doi: 10.1159/000488274. Epub 2018 Mar 16. PMID: 29558744.
12. Renziehausen A, Wang H, Rao B, Weir L, Nigro CL, Lattanzio L, Merlano M, Vega-Rioja A, Del Carmen Fernandez-Carranco M, Hajji N, Matin R, Harwood C, Li S, Sim VR, O'Neill K, Evans A, Thompson A, Szlosarek P, Fleming C, Stebbing J, Proby C, Tzagos AG, Syed N, Crook T. The renin angiotensin system (RAS) mediates bifunctional growth regulation in melanoma and is a novel target for therapeutic intervention. *Oncogene.* 2019 Mar;38(13):2320-2336. doi: 10.1038/s41388-018-0563-y. Epub 2018 Nov 26. PMID: 30478450.
13. Mansouri I, Botton J, Semenzato L, Haddy N, Zureik M. N-nitrosodimethylamine-Contaminated Valsartan and Risk of Cancer: A Nationwide Study of 1.4 Million Valsartan Users. *J Am Heart Assoc.* 2022 Dec 20;11(24):e8067. doi: 10.1161/JAHA.122.026739. Epub 2022 Dec 19. PMID: 36533625; PMCID: PMC9798794.
14. Sechi A, di Altobrando A, Cerciello E, Maietti E, Patrizi A, Savoia F. Drug intake and actinic keratosis: a case-control study. *Dermatol Pract Concept.* 2021;11(2):e2021031. DOI: <https://doi.org/10.5826/dpc.1102a31>
15. Tchernev G, Kordeva S, Marinov V, Batashki I, Batashki A, Patterson JW. Nitrosamines in antihypertensives, metformin and ranitidine as cofactors for melanoma and development of other cancers. Expert group opinion. *Port J Dermatol and Venereol.* 2022;80(4): 332–334. DOI: 10.24875/PJDV.22000014.

Lingual verrucous lymphangioma circumscriptum: exuberant case in an atypical location

Linfangioma verrucoso circunscrito na língua: caso exuberante em localização atípica

Isabella C. Mendes-Alexandre^{1,a*}, Carolina Souza-de Oliveira^{1,b}, Carla A. Ribeiro-Frota²,
Laísa E. de-Hollanda^{1,c}, Rebeca de-OAM-Martins¹, Vanessa R. Ferreira¹, and Luciana M. dos-Santos³

¹Division of Pediatric Dermatology, Hospital Universitário Getúlio Vargas, Manaus; ²Department of Pediatrics, Albert Einstein Hospital, São Paulo;

³Pediatric Dermatology Department, Hospital Universitário Getúlio Vargas, Manaus, Brasil

ORCID: ^a0000-0002-1460-3705; ^b0009-0005-6410-8357; ^c0000-0003-4240-0777

A 5-year-old girl had confluent, translucent papules on her tongue for 3 years (Fig. 1A and B). Biopsy revealed dilated lymphatic vessels with mononuclear and polymorphonuclear leukocytes (Fig. 1C).

Dermoscopy showed irregular translucent lakes with clear and serosanguineous content (Fig. 2A and B). After the biopsy, macroglossia worsened, and the papules showed necrotic content (Fig. 3A, B and C).

Treatment with triamcinolone acetonide ointment to reduce inflammation and systemic antibiotics was proposed. However, imaging exams to verify the extension of the condition and appropriate clinical treatment were not performed because the patient was lost to follow-up.

Discussion

Lingual lymphangioma circumscriptum (LC) is a benign condition that results from the formation of muscle-lined cysts, not connected to the lymphatic drainage system, projecting bumps on the skin or mucosa^{1,2}.

Congenital or acquired, LC targets the pediatric population and is diagnosed in children under 2 years

of age in about 90% of cases^{2,3}. The oral cavity is rarely involved, with the more common site being the tongue and, more rarely, palate, buccal mucosa, gingiva, the floor of the mouth, and lips³.

Clinically, LC is asymptomatic and has a good prognosis. However, cases in the head, neck, and oral cavity may be serious due to obstruction of the airways and death².

Lymphangioma circumscriptum (LC) treatment remains challenging because current therapeutic options are limited and have to be adapted according to the size of the lesion, its location and the range of anatomical structures and surroundings that are involved.

Treatment includes excision, cryotherapy, sclerotherapy, laser, radiofrequency, radiotherapy, and local steroids. Also, topical imiquimod with oral propranolol had success⁴.

TOPical sirolimus in linGual microcystic lymphatic malformation [TOPGUN] protocol, ongoing until 2025, is studying the efficacy and safety of topical sirolimus in the case of lymphangioma, which can pave the way into the first-line treatment for lingual microcystic lymphatic malformations⁵.

*Correspondence:

Isabella C. Mendes-Alexandre

E-mail: bellac_mendes@hotmail.com

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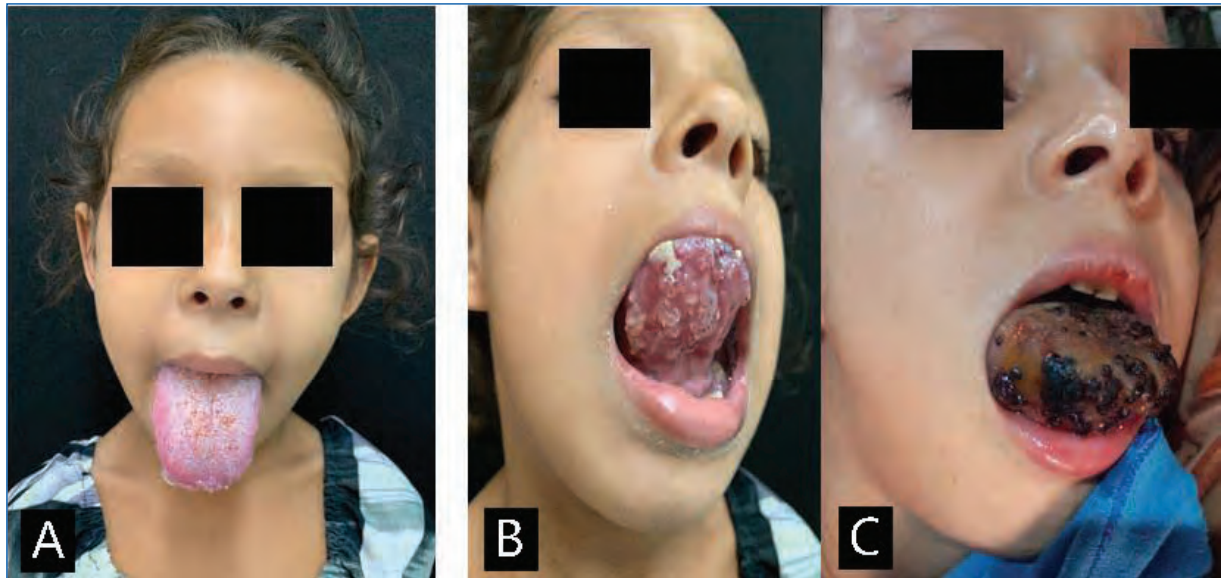


Figure 1. A: lesion in the anterior and posterior portion of the tongue before clinical treatment. **B:** multiple cystic lesions with serohemorrhagic content on the lingual dorsum before clinical treatment. **C:** complication 2 days after performing an incisional biopsy for diagnostic purposes.

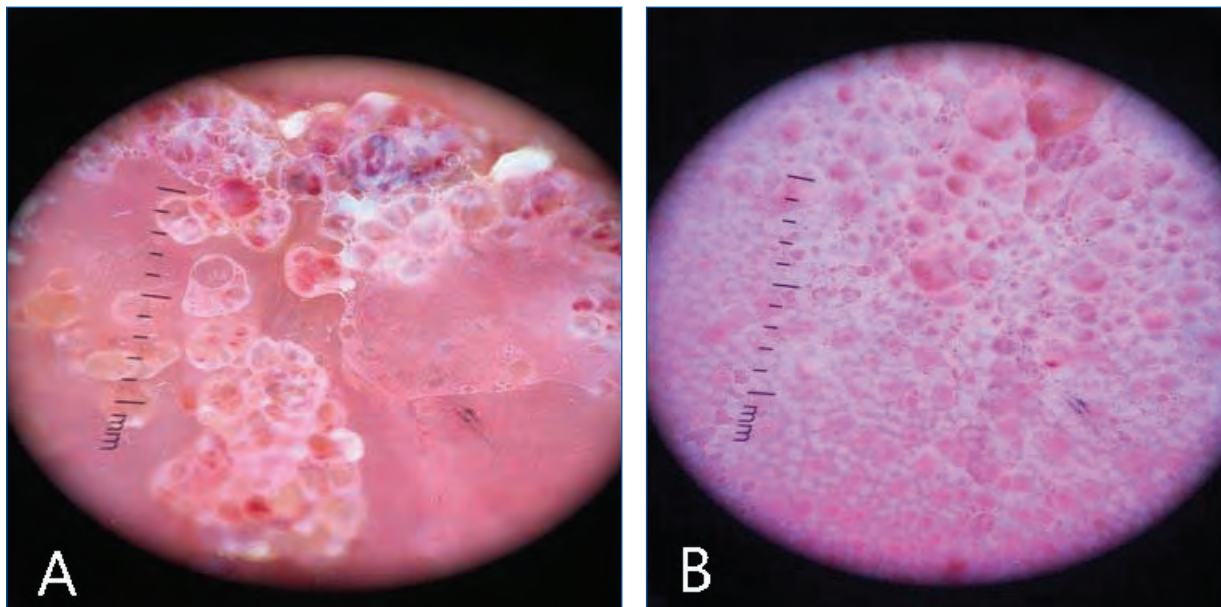


Figure 2. A: dermoscopy under polarized light of the dorsum of the tongue revealing papules with serohematic content and intermingled keratotic areas. **B:** papules separated by septum demonstrated by dermoscopy under polarized light.

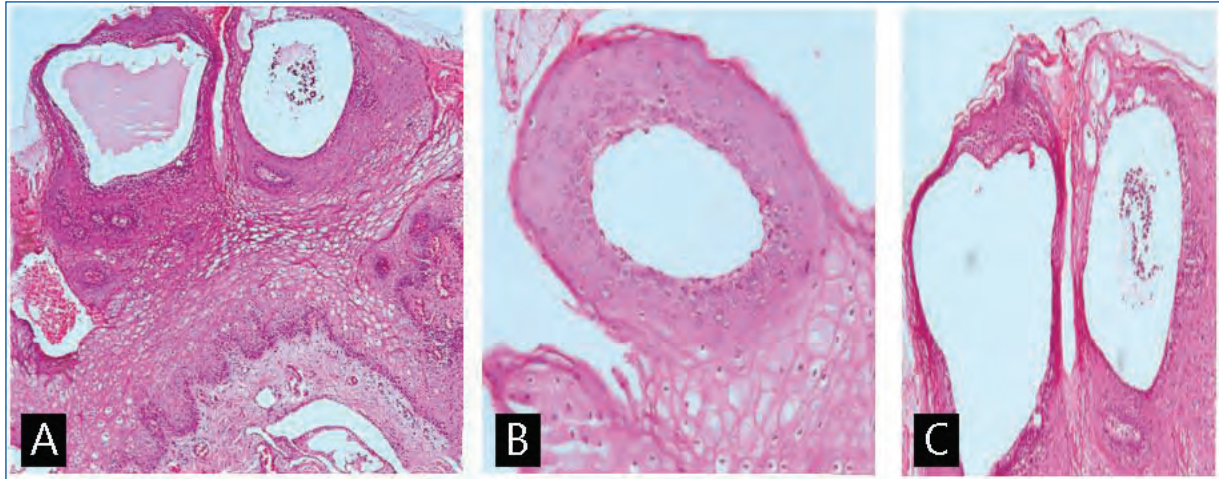


Figure 3. Histopathological features showing dilated lymphatic vessels not connected to the lymphatic network and thin, smooth muscle covered by flattened endothelium, without the presence of a capsule and amorphous lymphatic material inside. **A:** hematoxylin and eosin (H&E), 100× magnification, **B** and **C:** H&E stain, 200× magnification.

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References

1. Gupta AK, Ellis CN, Gorsulowsky DC. Chronic zosteriform eruption of the lower extremity. *Arch Dermatol.* 1988;124:267–8.
2. Magalhães AS, Dias GS, Rocha CRA, Dos Santos JHB, Fernandes TRMO. Linfangioma circunscrito em língua em paciente pediátrico: relato de caso. *Revista de Ensino, Ciência e Inovação em Saúde,* 2021
3. Kurude AA, Phiske MM, Kolekar KK, Nayak CS. Lymphangiomas: rare presentations in oral cavity and scrotum in pediatric age group. *Indian J Dermatol Venereol Leprol.* 2020;86:230.
4. Shah A, Chennareddy S, Sharma S, Sanghvi J, Tassavor B, Lewin JM. Surgical and non-surgical treatment modalities for lymphangioma circumscriptum. *Dermatol Online J.* 2022;28:19
5. Marchand A, Caille A, Gissot V, Giraudeau B, Lengelle C, Bourgoin H. et al. Topical sirolimus solution for lingual microcystic lymphatic malformations in children and adults (TOPGUN): study protocol for a multicenter, randomized, assessor-blinded, controlled, stepped-wedge clinical trial. *Trials.* 2022;23:557.

The great mimicker in dermatovenereology: a rare presentation

A grande imitadora da dermatovenereologia: uma apresentação rara

Cláudia Brazão^{1,a*}, Dora Mancha^{1,b}, Lanyu Sun^{1,c}, João Patrocínio^{1,d}, João Borges-Costa^{1,2,3,e}, and Paulo Filipe^{1,2,4,f}

¹Dermatology and Venereology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte; ²Dermatology and Venereology University Clinic, Faculty of Medicine, University of Lisbon; ³Institute of Hygiene and Tropical Medicine, Universidade Nova de Lisboa; ⁴Dermatology Research Unit, IMM João Lobo Antunes, University of Lisbon. Lisbon, Portugal

ORCID: ^a0000-0002-4485-7124; ^b0000-0002-6536-8936; ^c0000-0003-2148-1715; ^d0000-0002-2940-2463; ^e0000-0001-8903-209X; ^f0000-0002-7337-6493

A 31-year-old woman, Fitzpatrick's phototype V, with a previous history of Human Immunodeficiency Virus (HIV) infection under treatment with Highly Active Antiretroviral Therapy (HAART), presented to our Dermatology Emergency Department with a 2-week history of asymptomatic erythematous oral and perianal lesions. The patient reported unprotected sexual intercourse with a male partner 2 months before. She denied other systemic or local symptoms. On physical examination, there were asymptomatic, firm, flat-topped erythematous

plaques with a whitish surface located on the oral mucosa and perianal region (Fig. 1). Laboratory examination revealed a positive *Treponema pallidum* hemagglutination assay and a reactive Venereal Disease Research Laboratory test (1:64 dil). HIV viral load was undetectable and cluster of differentiation 4⁺ lymphocyte count was normal. Other sexually transmitted infections were excluded, namely hepatitis B and C, as well as gonorrhea and chlamydia (using urine polymerase chain reaction molecular testing). The diagnosis of oral and perianal



Figure 1. A: asymptomatic, flat-topped erythematous plaques with a whitish surface, located on the oral mucosa and **B:** perianal region.

***Correspondence:**

Cláudia Brazão
E-mail: claudiabrazaoemd@gmail.com

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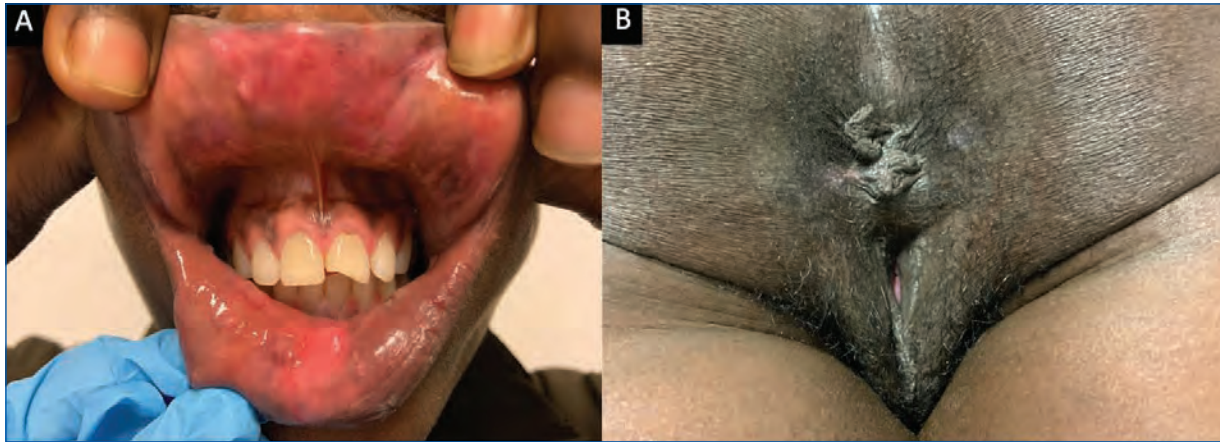


Figure 2. **A:** complete clinical resolution of the plaques on the oral mucosa and **B:** perianal region after treatment.

condylomata lata as the only manifestation of secondary syphilis was established. The patient was treated with one administration of intramuscular benzathine penicillin, 2.4 million units, with complete resolution of the lesions (Fig. 2). Syphilis is considered the great mimicker of dermatovenereology due to its numerous different presentations, especially in the secondary stage and in HIV patients, and its recognition can challenge even the most experienced clinician¹⁻³. Condylomata lata is a classic, though uncommon, presentation of secondary syphilis and can sometimes be its first and only clinical manifestation². Characteristically, it presents with nontender, whitish, and verrucous plaques located on the anogenital area, although extragenital locations may occur²⁻⁴. This case highlights that syphilis, in all its versatile and challenging presentations, should always be kept in mind in dermatology practice.

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References

1. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med.* 2020;382:845-54.
2. Barei F, Murgia G, Ramoni S, Cusini M, Marzano AV. Secondary syphilis with extragenital condyloma lata: a case report and review of the literature. *Int J STD AIDS.* 2022;33:1022-8.
3. Hua H, Zhu X, Yang L, Li M, Jiang P. Multiple condylomata lata: a case report. *Int J Dermatol.* 2008;47:56-8.
4. Dai T, Song NJ. An unusual case of oral condyloma lata. *Int J Infect Dis.* 2021;105:349-50.

Corticosteroids use in infantile hemangiomas: revisiting an old therapy

Utilização de corticosteroides em hemangiomas infantis: revisitando uma terapêutica antiga

Maria S. Pedro^{1,a*}, Beatriz S. Vala², and Cristina Amaro³

¹Department of Pediatrics, Centro Hospitalar Barreiro-Montijo, Setúbal; ²Department of Pediatrics, Centro Hospitalar de Leiria, Leiria; ³Department of Dermatology, Hospital CUF Descobertas, Lisbon. Portugal

^aORCID: 0000-0002-2032-7460

To the Editor,

Oral propranolol has replaced corticosteroids as the gold standard therapy for infantile hemangiomas (IH)¹⁻³. However, in some settings, such as ulceration, it might not be sufficient or even trigger or worsen ulceration^{2,4}. Treatment of refractory ulceration with oral propranolol is not consensual but brief adjunct courses of combined therapy with oral corticosteroids seem to accelerate improvement and promote healing^{2,4}.

A 2-month-old male, Caucasian with a previous history of preterm birth and low birth weight, was referred to a pediatric dermatology consultation due to a solitary superficial IH in the right flank. Topical timolol was used initially with good response and IH stabilization. However, at 6-month-old, rapid growth followed by central ulceration was noted, reaching, in the next month, a dimension of 4 per 3 cm with an ulcerative area of 1 cm. Despite being initiated at low doses (1 mg/kg daily), oral propranolol triggered ulceration worsening (Fig. 1). This led to add-up therapy with oral prednisolone (1.3 mg/kg daily) for 15 days (Fig. 2), followed by slow tapering doses for 15 additional days (total time of corticosteroids use 1 month), and concurrent slowly upward doses of propranolol. To facilitate ulceration healing, silicone and polyurethane pads were used (area of great friction by the diaper). Progressive healing of ulceration was noted with

complete reepithelization after 2 months (1 month of combined treatment followed by 1 month of propranolol alone) when therapeutic propranolol doses were reached (2 mg/kg daily). Weaning from propranolol was started after 3 additional months.

Since the discovery of propranolol's beneficial effects for IH and its efficacy and improved safety profile compared to systemic corticosteroids were proven, a switch to β -blockers as first-line treatment for complicated IH occurred¹⁻³. However, in some cases, such as IH with complex ulceration, propranolol in monotherapy might not be sufficient, and a brief course of oral corticosteroids might have an important adjunctive role^{2,4}. Lie and Püttgen reported two cases in which a 5 and 2-week full dose of oral prednisolone (2 mg/kg daily) followed by slow tapering doses over 4 additional weeks were used effectively to control and promote ulcer healing in IH with moderately deep ulceration refractory to propranolol and local therapies alone. In both cases, oral propranolol alone enabled IH volume and overall size to improve rapidly, although with no response regarding ulceration, which only occurred after add-up therapy with prednisolone². Meyer-Mueller et al. also described a case of a lip IH impairing feeding, in which progressive worsening of ulceration occurred despite oral propranolol doses up to 3 mg/kg daily. Adjunctive treatment with prednisolone (2 mg/kg

*Correspondence:

Maria S. Pedro

E-mail: saopedro.maria.pediatrica@gmail.com

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Figure 1. Ulcerated infantile hemangioma after 1-week treatment with propranolol.



Figure 2. Partial healing of ulceration after 2 weeks of combined therapy with propranolol and prednisolone at full dose (1.3 mg/kg daily).

daily) for 4 months enabled ulcer healing⁴. This effect was also seen in our case, in which add-up therapy with oral prednisolone led to ulceration control and progressive healing. The mechanism by which adding systemic corticosteroids to propranolol promotes rapid ulcer healing is not known and further studies are warranted². There is no standard protocol on the dose and duration of oral corticosteroid use^{1,2,5}, although 2-3 mg/kg daily has been shown to be effective, as seen in the previous reports. However, with multimodality treatment, lower corticosteroid doses are also likely to be effective^{2,5}, as observed in our case. In neither case (reported previously in literature nor ours), recurrence of ulceration occurred after suspension of oral corticosteroids, and oral propranolol was maintained in monotherapy for additional months facilitating IH regression. Despite concerns regarding the dual use of these medications and hypoglycemia risk during corticosteroid weaning^{6,7}, this complication was only reported once and was attributed to adrenal suppression due to prolonged use of high corticosteroid doses⁶. Regarding the additional use of corticosteroids as a combined treatment for IH, Aly et al. also studied the usage of oral propranolol alone versus combined with 2-week

oral prednisolone “priming”, showing a statistically superior reduction in IH size, thus recommending its use for life or function-threatening IH⁸. Gnarr et al. also found in a case series of three patients with PHACE syndrome that the combination of low-dose propranolol and low-dose prednisolone showed a more rapid and sustained improvement of segmental hemangiomas than monotherapy⁷. Another important aspect highlighted by our case is that ulcerated IH might also benefit from lower and slowly titrated doses of propranolol, since propranolol might worsen ulceration^{1-4,9}, due to the proposed mechanism of decreased tissue perfusion through vasoconstriction^{3,9}. As such, doses ≤ 1 mg/kg daily should be considered as an initial approach to ulcerated IH, with slow upward titration ideally after healing is well under way^{3,9}. In conclusion, we considered that oral corticosteroids might still play a valuable role in IH management, recommending its use as combined therapy if significant or painful ulceration persists after 2-4 weeks of treatment with oral propranolol.

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References

1. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, Blei F, Greene AK, et al. Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics*. 2019;143:e20183475.
2. Lie E, Püttgen KB. Corticosteroids as an adjunct to propranolol for infantile haemangiomas complicated by recalcitrant ulceration. *Br J Dermatol*. 2017;176:1064-7.
3. Polites SF, Rodrigue BB, Chute C, Hammill A, Dasgupta R. Propranolol versus steroids for the treatment of ulcerated infantile hemangiomas. *Pediatr Blood Cancer*. 2018;65:e27280.
4. Meyer-Mueller C, Nicholson C, Polcari I, Boull C, Maguiness S. Worsening ulceration of infantile hemangioma after initiation or escalation of propranolol. *Pediatr Dermatol*. 2022;39:255-9.
5. Nieuwenhuis K, de Laat PC, Janmohamed SR, Madern GC, Oranje AP. Infantile hemangioma: treatment with short course systemic corticosteroid therapy as an alternative for propranolol. *Pediatr Dermatol*. 2013;30:64-70.
6. Breur JM, de Graaf M, Breugem CC, Pasmans SG. Hypoglycemia as a result of propranolol during treatment of infantile hemangioma: a case report. *Pediatr Dermatol*. 2011;28:169-1.
7. Gnarr M, Solman L, Harper J, Batul Syed S. Propranolol and prednisolone combination for the treatment of segmental haemangioma in PHACES syndrome. *Br J Dermatol*. 2015;173:242-6.
8. Aly MM, Hamza AF, Abdel Kader HM, Saafan HA, Ghazy MS, Ragab IA. Therapeutic superiority of combined propranolol with short steroids course over propranolol monotherapy in infantile hemangioma. *Eur J Pediatr*. 2015;174:1503-9.
9. Fernández Faith E, Shah S, Witman PM, Harfmann K, Bradley F, Blei F, et al. Clinical features, prognostic factors and treatment interventions for ulceration in patients with infantile hemangioma. *JAMA Dermatol*. 2021;157:566-2.

The potential use of artificial intelligence in the evaluation and treatment of patients with psoriasis

A potencial utilização da inteligência artificial na avaliação e tratamento de doentes com psoríase

Joana Vieitez-Frade^{1,a*} and Paulo Filipe^{1,2,3}

¹Dermatology and Venereology Department, Centro Hospitalar Universitário Lisboa Norte, EPE; ²Dermatology and Venereology University Clinic, Faculdade de Medicina da Universidade de Lisboa; ³Dermatology Research Unit, IMM Joao Lobo Antunes, Universidade de Lisboa, Lisbon, Portugal
^aORCID: 0000-0002-5471-7889

Dear Editor,

Artificial intelligence (AI) is a computer science that focuses on developing algorithmic programs that aim to reproduce human cognition and processes involved in the analysis of complex data. Recent advances in this field have improved current medical practice, particularly helpful in basic research, diagnosis accuracy, image recognition, treatment decision, and surgical assistance. Several AI studies have been focusing on dermatological disorders such as skin cancer, inflammatory dermatosis, and onychomycosis¹.

Psoriasis is an inflammatory skin disease that has been widely studied, although the molecular mechanisms and pathophysiology are not yet fully understood. AI has been implicated as a relevant and innovative tool in molecular biology, clinical assessment, customize treatment protocols, and outcome predictions in psoriatic patients².

Artificial intelligence (AI) has been tested for the clinical and histopathological diagnosis of psoriasis. For example, Shrivastava et al. achieved 99% clinical diagnostic accuracy with a support vector machine model after classifying 540 skin images¹. In another study, the algorithm classified 8,021 images of eight common disorders (lichen planus, lupus erythematosus, basal cell

carcinoma, squamous cell carcinoma, atopic dermatitis, pemphigus, psoriasis, and seborrheic keratosis), with a misdiagnosis psoriasis rate of 3% compared to 27% by dermatologists³. Furthermore, similar results were demonstrated between convolutional neural networks and dermatologists when comparing their performance in classifying dermoscopic images of psoriasis⁴. Pal et al. presented a computational framework that detects Munro's microabscesses in the epidermal stratum corneum of the skin from biopsy images⁵.

The three most used indicators to evaluate psoriasis severity are the psoriasis area severity index (PASI), body surface area (BSA), and Physician Global Assessment (PGA). AI use in BSA and PASI measurements could greatly reduce the workload of doctors while ensuring a high degree of repeatability and standardization². These tools could also allow long-distance follow-up of patients with psoriasis, which would be particularly interesting for locations with low access to differentiated health care. Currently, machine learning-based algorithms are already available to determine BSA scores, which have shown promising results, as they overcome dermatologists in measurement accuracy⁶. Besides no algorithm has been validated for scoring independently PASI score yet, recently Huang

*Correspondence:

Joana Vieitez-Frade
E-mail: joanamvfrade@gmail.com

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et al. proposed an image-AI-based PASI-estimating model that outperformed the average performance of 43 experienced dermatologists².

In addition to these applications, several recent studies report the usefulness of AI in the timely diagnosis of psoriatic comorbidities, including psoriatic arthritis, which may influence the prognosis of these patients. Mulder et al. found that by combining comprehensive peripheral blood immune cell flow cytometry with machine learning techniques, they were able to distinguish immune cell profiles that could differentiate patients with psoriatic arthritis who would benefit from timely referral to a rheumatology clinic⁷.

Artificial intelligence (AI) has also shown promising results in the development of predictive models that can help identify psoriatic patients who are likely to respond to specific treatments. By analyzing data on a patient's medical history, genetics, and disease activity, AI algorithms can identify the most effective treatment options for that individual. This approach has the potential to improve patient outcomes and reduce the risk of side effects associated with ineffective treatments. Damiani et al. developed a predictive model using artificial neural networks on patients treated with secukinumab, predicting fast responders based on 15 continuous variables, such as BSA, white blood count, hemoglobin, platelets, and liver function tests⁸. AI has also been used in order to identify drug interactions based on semantic predictions extracted from medical databases and predict long-term responses to biologics^{9,10}.

Despite these promising applications, there are also challenges associated with the use of AI in psoriasis. One major challenge is the need for high-quality data to train these algorithms. This requires large datasets of patient information, which may be difficult to obtain in some cases. Additionally, there are concerns about the ethical and regulatory implications of using AI in healthcare, particularly in the context of patient privacy and data security¹.

In conclusion, AI is developing at lightning speed in the dermatological field, so its use in clinical practice is expected to increase exponentially in the coming years.

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References

1. Hogarty DT, Su JC, Phan K, Attia M, Hossny M, Nahavandi S, et al. Artificial intelligence in dermatology-where we are and the way to the future: a review. *Am J Clin Dermatol*. 2020;21:41-7.
2. Yu K, Syed MN, Bernardis E, Gelfand JM. Machine learning applications in the evaluation and management of psoriasis: a systematic review. *J Psoriasis Psoriatic Arthritis*. 2020;5:147-59.
3. Huang K, Wu X, Li Y, Lv C, Yan Y, Wu Z, et al. Artificial intelligence-based psoriasis severity assessment: real-world study and application. *J Med Internet Res*. 2023;25:e44932.
4. Yang Y, Wang J, Xie F, Liu J, Shu C, Wang Y, et al. A convolutional neural network trained with dermoscopic images of psoriasis performed on par with 230 dermatologists. *Comput Biol Med*. 2021;139:104924.
5. Pal A, Chaturvedi A, Chandra, A, Chatterjee R, Senapati S, Frangi AF, et al. Multi-instance capsule network for machine inspection of munro's microabscess. *Comput Biol Med*. 2022;140:105071.
6. Lee WH, Lee S, Kim J, Han J, Kim Y, Kim J, et al. Measurement of psoriasis-affected area with artificial neural network. *J Am Acad Dermatol*. 2023;88:731-32.
7. Mulder MLM, He X, Van-den-Reek JMPA, Urbano PCM, Kaffa C, Wang X, et al. Blood-based immune profiling combined with machine learning discriminates psoriatic arthritis from psoriasis patients. *Int J Mol Sci*. 2021;22:10990.
8. Damiani G, Conic RRZ, Pigatto PDM, Carrera C, Franchi C, Cattaneo A, et al. Predicting Secukinumab Fast-Responder Profile in Psoriatic Patients: Advanced Application of Artificial-Neural-Networks (ANNs). *J Drugs Dermatol*. 2020;19:1241-1246.
9. Zhang R, Cairelli MJ, Fiszman M, Rosembat G, Kilicoglu H, Rindflesch T, et al. Using semantic predictions to uncover drug-drug interactions in clinical data. *J Biomed Inform*. 2014;49:134-47.
10. Emam S, Du AX, Surmanowicz P, Thomsen SF, Greiner R, Gnidecki R. Predicting the long-term outcomes of biologics in patients with psoriasis using machine learning. *Br J Dermatol*. 2020;182:1305-7.