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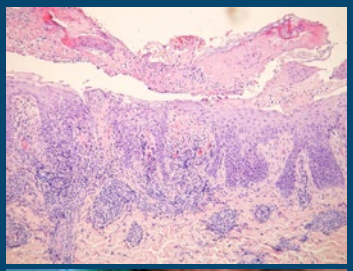

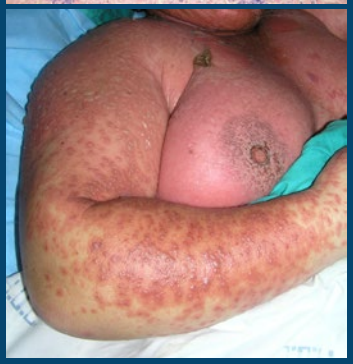

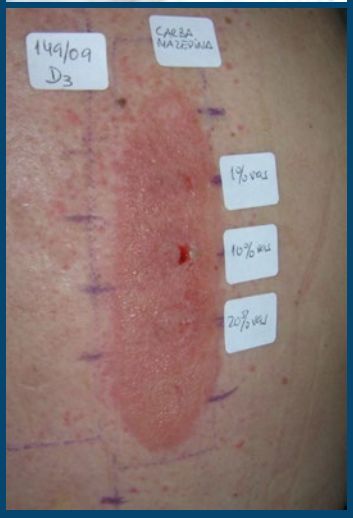

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RESULTADOS PARTILHADOS

FELICIDADE PARTILHADA

RESULTADOS CONSISTENTES DE SEGURANÇA E EFICÁCIA DEMONSTRADOS NA ROTINA DA PRÁTICA CLÍNICA[14-16]

MAIS DE 260.000 DOENTES COM DERMATITE ATÓPICA TRATADOS EM TODO O MUNDO[11]

- DUPIXENT® é o primeiro **imunomodulador a inibir especificamente a sinalização da IL-4 e IL-13**, reduzindo assim a inflamação do tipo 2 persistente, subjacente à dermatite atópica[1,2]
- **Melhoria rápida e sustentada** na extensão e gravidade das lesões, intensidade do prurido e na qualidade de vida[1,3,4,5,6–10,12,14]
- **Perfil de segurança** estabelecido em **doentes jovens, com idade ≥ 6 anos — Sem necessidade de monitorização** para toxicidade específica ao nível dos órgãos[1]
  - As reações adversas mais frequentes foram reações no local de injeção, conjuntivite, blefarite e herpes oral[1]

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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO ▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas. Para saber como notificar reações adversas, ver secção 4.8. do RCM completo. **Nome do medicamento** Dupixent 300 mg solução injetável em seringa pré-cheia; Dupixent 300 mg solução injetável em caneta pré-cheia; Dupixent 200 mg solução injetável em seringa pré-cheia; Dupixent 200 mg solução injetável em caneta pré-cheia. **Composição Qualitativa e Quantitativa** Dupixent 300 mg solução injetável em seringa pré-cheia ou caneta pré-cheia. Cada seringa pré-cheia ou caneta pré-cheia de utilização única contém 300 mg de dupilumab em 2 ml de solução (150 mg/ml). Dupilumab 200 mg solução injetável em seringa pré-cheia ou caneta pré-cheia. Cada seringa pré-cheia de utilização única contém 200 mg de dupilumab em 1,14 ml de solução (175 mg/ml). Dupilumab é um anticorpo monoclonal totalmente humano contra o recetor alfa da interleucina (IL)-4 que inibe a sinalização IL-4/IL-13, produzido em células de ovário de hamster chinês (CHO) por tecnologia de ADN recombinante. Lista completa de excipientes, ver secção 6.1. do RCM completo. **Forma Farmacêutica** Solução injetável (injetável). Solução estéril transparente a ligeiramente opalescente, incolor a amarelo pálido, isenta de partículas visíveis, com um pH aproximado de 5,9. **Indicações terapêuticas** Dupixent 200 mg e 300 mg: Dermatite atópica *Adultos e adolescentes* Dupixent é indicado para o tratamento de dermatite atópica moderada a grave em adultos e adolescentes com idade igual ou superior a 12 anos que são candidatos a terapêutica sistémica. *Crianças dos 6 aos 11 anos* de idade Dupixent é indicado para o tratamento de dermatite atópica grave em crianças dos 6 aos 11 anos de idade que são candidatos a terapêutica sistémica. Asma Dupixent é indicado em adultos e adolescentes com idade igual ou superior a 12 anos como tratamento complementar de manutenção para asma grave com inflamação tipo 2 caraterizada por eosinófilos elevados no sangue e/ou fração exalada de óxido nítrico (FeNO) aumentada, ver secção 5.1 do RCM completo, que são inadequadamente controlados apesar das doses elevadas de corticosteroides inalados associados a outro medicamento para tratamento de manutenção. Dupixent 300 mg: Rinossinusite crónica com polipose nasal (CRSwNP). Dupixent é indicado como terapia complementar com corticosteróides intranasais para o tratamento de adultos com CRSwNP grave, para quem a terapia com corticosteróides sistémicos e/ou cirurgia não fornece controlo adequado da doença. **Posologia e modo de administração** O tratamento deve ser iniciado por profissionais de saúde com experiência no diagnóstico e tratamento de condições para os quais o dupilumab está indicado (ver secção 4.1 do RCM completo). **Posologia** Dermatite atópica *Adultos* A dose recomendada de dupilumab para doentes adultos é uma dose inicial de 600 mg (duas injeções de 300 mg), seguida por 300 mg administrados em semanas alternadas sob a forma de injeção subcutânea. *Adolescentes (12 anos 17 anos de idade)* A dose recomendada de dupilumab para doentes adolescentes dos 12 aos 17 anos de idade está especificada na Tabela 1. **Tabela 1: Dose de dupilumab para administração subcutânea em doentes adolescentes dos 12 aos 17 anos de idade com dermatite atópica.** Peso Corporal do Doente: menos de 60 kg: Dose Inicial: 400 mg (duas injeções de 200 mg). Doses Subsequentes (em semanas alternadas): 200 mg. 60 kg ou mais: Dose Inicial: 600 mg (duas injeções de 300 mg). Doses Subsequentes (em semanas alternadas): 300 mg. *Crianças dos 6 aos 11 anos de idade* A dose recomendada de dupilumab para crianças dos 6 aos 11 anos de idade está especificada na Tabela 2. **Tabela 2: Dose de dupilumab para administração subcutânea em crianças dos 6 aos 11 anos de idade com dermatite atópica.** Peso Corporal do Doente: de 15kg a menos de 60 kg: Dose Inicial: 300 mg (uma injeção de 300 mg) no Dia 1, seguida de 300 mg no Dia 15. Doses Subsequentes: 300 mg a cada 4 semanas (Q4W) * começando 4 semanas após a dose do Dia 15. 60 kg ou mais: Dose Inicial: 600 mg (duas injeções de 300 mg). Doses Subsequentes: 300 mg em semanas alternadas (Q2W). Dupilumab pode ser utilizado com ou sem corticosteroides tópicos. Poderão ser utilizados inibidores da calcineurina tópicos, mas devem ser reservados apenas para as áreas problemáticas, tais como a face, o pescoço e as áreas intertriginosas e genitais. Deve ter-se em consideração a interrupção do tratamento em doentes que não tenham apresentado resposta após 16 semanas de tratamento para a dermatite atópica. Alguns doentes com resposta parcial inicial podem subsequentemente melhorar com a continuação do tratamento além das 16 semanas. Se for necessária a interrupção do tratamento com dupilumab, os doentes podem ser tratados novamente com sucesso. Asma A dose recomendada de dupilumab para adultos e adolescentes (idade igual ou superior a 12 anos) é: • Em doentes com asma grave e terapêutica oral com corticosteróides ou doentes com asma grave e dermatite atópica comórbida de moderada a grave ou em adultos com rinossinusite crónica com polipose nasal comórbida grave, uma dose inicial de 600 mg (duas injeções de 300 mg), seguida de 300 mg administradas em semanas alternadas sob a forma de injeção subcutânea. • Para todos os outros doentes, uma dose inicial de 400 mg (duas injeções de 200 mg), seguida de 200 mg administradas em semanas alternadas sob a forma de injeção subcutânea. Os doentes tratados concomitantemente com corticosteróides orais, podem reduzir a sua dose de esteróides, uma vez que tenha ocorrido uma melhoria clínica com o dupilumab (ver secção 5.1 do RCM completo). A redução dos esteróides deve ser realizada gradualmente (ver secção 4.4 do RCM completo). Dupilumab destina-se a tratamento de longo prazo. Deve ser considerada a necessidade de terapia continuada pelo menos numa base anual, conforme determinado pela avaliação médica do nível de controlo da asma do doente. Dupixent 300 mg: *Rinossinusite crónica com polipose nasal (CRSwNP)* A dose recomendada de dupilumab para doentes adultos é uma dose inicial de 300 mg seguida de 300 mg administradas em semanas alternadas. O dupilumab destina-se a tratamento de longo prazo. Deve ser considerada a interrupção do tratamento em doentes que não apresentem resposta após 24 semanas de tratamento para a CRSwNP. Alguns doentes com resposta parcial inicial podem melhorar posteriormente com o tratamento continuado além das 24 semanas. Dose esquecida Caso uma dose seja esquecida, administrar a dose logo que possível. Em seguida, retomar a dosagem à hora marcada habitual. Populações especiais *Idosos (≥65 anos)* Não é recomendado qualquer ajuste posológico para os doentes idosos (ver secção 5.2 do RCM completo). *Compromisso renal* Não é necessário qualquer ajuste posológico nos doentes com insuficiência renal ligeira ou moderada. Estão disponíveis dados muito limitados sobre doentes com insuficiência renal grave (ver secção 5.2 do RCM completo). *Compromisso hepático* Não estão disponíveis dados sobre doentes com insuficiência hepática (ver secção 5.2 do RCM completo). *Peso corporal* Dupixent 200 mg: Não é recomendado qualquer ajuste posológico para o peso corporal em doentes com asma com idade igual ou superior a 12 anos ou em adultos com dermatite atópica (ver secção 5.2 do RCM completo). Dupixent 300 mg: Não é recomendado qualquer ajuste posológico para o peso corporal em doentes com asma com idade igual ou superior a 12 anos ou em adultos com dermatite atópica ou CRSwNP (ver secção 5.2 do RCM completo). Em doentes dos 12 anos aos 17 anos de idade com dermatite atópica, a dose recomendada em semanas alternadas é de 200 mg (< 60 kg) ou 300 mg (≥ 60 kg). Em doentes dos 6 aos 11 anos de idade com dermatite atópica, as doses recomendadas são de 300 mg Q4W com a possibilidade de aumentar para 200 mg Q2W (de 15 kg a < 60 kg) e 300 mg Q2W (≥ 60 kg). *Doentes pediátricos* Dupixent 300 mg: A segurança e eficácia de dupilumab em crianças com dermatite atópica com menos de 6 anos de idade não foram estabelecidas. A segurança e eficácia de dupilumab em crianças com peso corporal < 15 kg não foram estabelecidas (ver secção 5.2 do RCM completo). Não existem dados disponíveis. Dupixent 200 mg: A segurança e eficácia de dupilumab em crianças com dermatite atópica com menos de 12 anos de idade não foram estabelecidas. A segurança e eficácia de dupilumab em crianças com peso corporal < 15 kg não foram estabelecidas (ver secção 5.2). Não existem dados disponíveis. A segurança e eficácia de dupilumab em crianças com asma grave com menos de 12 anos de idade não foram estabelecidas (ver secção 5.2 do RCM completo). Não existem dados disponíveis. Dupixent 300 mg: Normalmente, a CRSwNP não ocorre em crianças. A segurança e eficácia em crianças com CRSwNP com idade inferior a 18 anos não foram estabelecidas (ver secção 5.2 do RCM completo). Não existem dados disponíveis. Modo de administração Via subcutânea. A caneta pré-cheia de dupilumab não se destina a ser utilizada em crianças com menos de 12 anos de idade. Para crianças dos 6 aos 11 anos de idade com dermatite atópica, a seringa pré-cheia de dupilumab é a apresentação apropriada para administração a essa população. Dupilumab é administrado por injeção subcutânea na coxa ou no abdómen, excetuando na área de 5 cm à volta do umbigo. Se for outra pessoa a administrar a injeção, também pode ser utilizada a região superior do braço. Dupixent 200 mg: Para a dose inicial de 400 mg, administrar duas injeções de 200 mg consecutivamente em locais de injeção diferentes. Dupixent 300 mg: Para a dose inicial de 600 mg, administrar duas injeções de 300 mg de Dupixent consecutivamente em locais de injeção diferentes. Recomenda-se que vá alternando o local de injeção. Dupilumab não deve ser injetado em pele sensível ao toque, lesionada ou que tenha equimoses ou cicatrizes. Os doentes podem autoinjetar dupilumab ou o prestador de cuidados do doente pode administrar dupilumab, caso o seu profissional de saúde determine que tal é apropriado. Deve ser proporcionada formação adequada aos doentes e/ou aos prestadores de cuidados sobre a preparação e a administração de dupilumab antes de utilizar de acordo com a secção Instruções de utilização do folheto informativo. **Contraindicações** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1 do RCM completo. **Efeitos indesejáveis** *Resumo do perfil de segurança* As reações adversas mais frequentes em estudos clínicos controlados com dupilumab na dermatite atópica, asma e CRSwNP foram reações no local de injeção (incluindo eritema, edema, prurido, dor e inchaço), conjuntivite, artralgia, herpes oral, e eosinofilia. Foram notificados casos raros de reações de doença do soro, reações do tipo doença do soro, reação anafilática, e queratite ulcerosa (ver secção 4.4 do RCM completo). Em estudos de monoterapia na dermatite atópica, em adultos, a proporção de doentes que descontinuaram o tratamento devido a acontecimentos adversos foi de 1,9% no grupo de placebo, de 1,9% no grupo de dupilumab 300 mg Q2W e de 1,5% no grupo de dupilumab 300 mg QW. No estudo com CST concomitantes em adultos, a proporção de doentes que descontinuaram o tratamento devido a acontecimentos adversos foi de 7,6% no grupo de placebo + CST, de 1,8% no grupo de dupilumab 300 mg Q2W + CST e de 2,9% no grupo de dupilumab 300 mg QW + CST. Nos estudos de asma DRI12544 e QUEST, a proporção de doentes que descontinuaram o tratamento devido a acontecimentos adversos foi de 4,3% no grupo de placebo, de 3,2% no grupo de dupilumab 200 mg Q2W e de 6,1% no grupo de dupilumab 300 mg Q2W. Nos estudos SINUS-24 e SINUS-52 de CRSwNP, a proporção de doentes que descontinuaram o tratamento devido a acontecimentos adversos foi de 2,0% no grupo de dupilumab 300 mg Q2W e de 4,6% no grupo de placebo. *Lista tabelada de reações adversas* O dupilumab foi estudado em 12 ensaios clínicos aleatorizados e controlados por placebo, incluindo dermatite atópica, asma e doentes com CRSwNP. Os principais estudos controlados envolveram 4.206 doentes que receberam dupilumab e 2.326 doentes que receberam placebo durante o período controlado. Listadas na Tabela 3 estão as reações adversas observadas em estudos clínicos na dermatite atópica, asma e CRSwNP e/ou após o início da comercialização, apresentadas por classe de sistema de órgãos e frequência, utilizando as seguintes categorias: muito frequentes (≥ 1/10); frequentes (≥ 1/100, < 1/10); pouco frequentes (≥ 1/1.000, < 1/100); raras (≥ 1/10.000, < 1/1.000); muito raras (< 1/10.000). **Tabela 3 Lista de reações adversas. Classe de sistemas de órgãos MedDRA:** Infeções e infestações. **Frequência**: Frequentes. **Reação adversa**: Conjuntivite*; Herpes oral*. **Classe de sistemas de órgãos MedDRA**: Doenças do sangue e do sistema linfático. **Frequência**: Frequentes. **Reação adversa**: Eosinofilia. **Classe de sistemas de órgãos MedDRA**: Doenças do sistema imunitário. **Frequência**: Raros. **Reação adversa**: Reação da doença do soro; Reação do tipo doença do soro; Reação anafilática. **Frequência**: Pouco frequentes. **Reação adversa**: Angioedema. **Classe de sistemas de órgãos MedDRA**: Afeções oculares. **Frequência**: Frequentes. **Reação adversa**: Conjuntivite alérgica*. **Frequência**: Pouco frequentes. **Reação adversa**: Prurido ocular*†; Blefarite*†; Queratite*; Olho seco*†. **Frequência**: Raros. **Reação adversa**: Queratite ulcerativa*†. **Classe de sistemas de órgãos MedDRA**: Afeções dos tecidos cutâneos e subcutâneos. **Frequência**: Pouco frequentes. **Reação adversa**: Erupção cutânea facial. **Classe de sistemas de órgãos MedDRA**: Afeções musculosqueléticas e dos tecidos conjuntivos. **Frequência**: Frequentes. **Reação adversa**: Artralgia. **Classe de sistemas de órgãos MedDRA**: Perturbações gerais e alterações no local de administração. **Frequência**: Frequentes. **Reação adversa**: Reações no local de injeção (incluindo eritema, edema, prurido, dor e inchaço). * Afeções oculares e herpes oral ocorreram predominantemente em estudos de dermatite atópica. † A frequência de prurido ocular, blefarite e olho seco era frequente e da queratite ulcerativa era pouco frequente em estudos de dermatite atópica. Dupixent 200 mg e 300 mg: Descrição de reações adversas selecionadas nas indicações de dermatite atópica, asma e CRSwNP. *Hipersensibilidade* Foram comunicados casos de reação anafilática, angioedema e de doença do soro/reações do tipo doença do soro após a administração de dupilumab (ver secção 4.4 do RCM completo). *Acontecimentos relacionados com conjuntivite e queratite* Conjuntivite e queratite ocorreram mais frequentemente em doentes com dermatite atópica que receberam dupilumab, comparado com placebo em estudos de dermatite atópica. A maioria dos doentes com conjuntivite ou queratite recuperou ou estava a recuperar durante o período de tratamento. No estudo de dermatite atópica a longo prazo OLE (AD-1225) aos três anos, as respetivas taxas de conjuntivite e queratite permaneceram semelhantes às do grupo tratado com dupilumab nos estudos de dermatite atópica controlados com placebo. Nos doentes com asma, a frequência de conjuntivite e queratite foi baixa e semelhante entre o dupilumab e o placebo. Nos doentes com CRSwNP, a frequência de conjuntivite foi superior no dupilumab do que no placebo, embora menor do que a observada nos doentes com dermatite atópica. Não existiram casos de queratite notificados no programa de desenvolvimento de CRSwNP (ver secção 4.4 do RCM completo). *Eczema herpético* Foi comunicado eczema herpético em < 1% dos grupos de dupilumab e em < 1% do grupo de placebo nos estudos de monoterapia, em adultos, com dermatite atópica de 16 semanas. No estudo em adultos de dupilumab + CST de 52 semanas, foi comunicado eczema herpético em 0,2% do grupo de dupilumab + CST e em 1,9% do grupo de placebo + CST. As taxas permaneceram estáveis no estudo a longo prazo OLE (AD-1225) aos três anos. *Eosinofilia* Os doentes tratados com dupilumab tiveram um aumento médio inicial maior do que o valor basal na contagem de eosinófilos em comparação com os doentes tratados com placebo. A contagem de eosinófilos diminuiu para perto dos níveis basais durante o tratamento do estudo e voltou aos valores basais durante o estudo de extensão aberto de segurança da asma (TRAVERSE). Os níveis médios de eosinófilos sanguíneos diminuíram abaixo dos níveis basais, na semana 20, e mantiveram-se, até aos 3 anos, no estudo a longo prazo OLE (AD-1225). Foi notificado tratamento emergente para eosinofilia (≥ 5,000 células/mcl) em <2% dos doentes tratados com dupilumab e < 0,5% nos doentes tratados com placebo (ver secção 4.4 do RCM completo). *Infeções* Nos estudos clínicos, em adultos, de dermatite atópica em monoterapia de 16 semanas, foram comunicadas infeções graves em 1,0% dos doentes tratados com placebo e em 0,5% dos doentes tratados com dupilumab. No estudo CHRONOS, em adultos, de dermatite atópica de 52 semanas, foram reportadas infeções graves em 0,6% dos doentes tratados com placebo e em 0,2% dos doentes tratados com dupilumab. As taxas de infeções graves permaneceram estáveis até aos 3 anos no estudo a longo prazo OLE (AD-1225). Não se observou aumento na incidência geral de infeções com dupilumab em comparação com placebo no grupo de segurança dos estudos clínicos de asma. No grupo de segurança de 24 semanas, foram notificadas infeções graves em 1,0% dos doentes tratados com dupilumab e em 1,1% dos doentes tratados com placebo. No estudo QUEST de 52 semanas, foram notificadas infeções graves em 1,3% dos doentes tratados com dupilumab e em 1,4% dos doentes tratados com placebo. Não se observou aumento na incidência geral de infeções com dupilumab em comparação com placebo no grupo de segurança dos estudos clínicos de CRSwNP. No estudo SINUS-52 de 52 semanas, foram notificadas infeções graves em 1,3% dos doentes tratados com dupilumab e em 1,3% dos doentes tratados com placebo. *Imunogenicidade* Como todas as proteínas terapêuticas, existe um potencial para imunogenicidade com dupilumab. As respostas de Anticorpos Antifármacos (AAF) não foram, de forma geral, associadas a um impacto na exposição, na segurança ou na eficácia de dupilumab. Aproximadamente 5% dos doentes com dermatite atópica, asma ou CRSwNP que receberam dupilumab 300 mg Q2W durante 52 semanas desenvolveram AAF ao dupilumab; aproximadamente 2% exibiram respostas persistentes de AAF e aproximadamente 2% apresentaram anticorpos neutralizantes. Foram observados resultados semelhantes em doentes pediátricos (6 aos 11 anos de idade) com dermatite atópica que receberam dupilumab 200 mg Q2W ou 300 mg Q4W durante 16 semanas. Foram observadas respostas de AAF semelhantes em doentes adultos com dermatite atópica tratados com dupilumab até aos 3 anos no estudo a longo prazo OLE (AD-1225). Aproximadamente 16% dos doentes adolescentes com dermatite atópica que receberam dupilumab 300 mg ou 200 mg Q2W durante 16 semanas desenvolveram anticorpos ao dupilumab; aproximadamente 3% exibiram respostas persistentes de AAF e aproximadamente 5% apresentaram anticorpos neutralizantes. Aproximadamente 9 % dos doentes com asma que receberam dupilumab 200 mg Q2W durante 52 semanas desenvolveram anticorpos ao dupilumab; aproximadamente 4% exibiram respostas persistentes de AAF e aproximadamente 4% apresentaram anticorpos neutralizantes. Independentemente da idade ou população, aproximadamente 2 a 4 % dos doentes nos grupos placebo foram positivos para anticorpos ao dupilumab; aproximadamente 2 % apresentaram resposta persistente de AAF e aproximadamente 1 % apresentaram anticorpos neutralizantes. Menos de 1 % dos doentes que receberam dupilumab em regime de dosagens aprovadas apresentaram respostas de AAF com titulação elevada associadas a exposição e eficácia reduzidas. Além disso, houve um doente com doença do soro e um com reação do tipo doença do soro (<0,1%) associadas a titulações elevadas de AAF (ver secção 4.4 do RCM completo). População pediátrica Dermatite atópica. Adolescentes dos 12 aos 17 anos de idade. A segurança do dupilumab foi avaliada num estudo de 250 doentes dos 12 aos 17 anos de idade com dermatite atópica moderada a grave (AD-1526). O perfil de segurança do dupilumab nestes doentes, que foram acompanhados até à semana 16, foi semelhante ao perfil de segurança dos estudos em adultos com dermatite atópica. Asma. Um total de 107 adolescentes dos 12 aos 17 anos com asma foram incluídos no estudo QUEST de 52 semanas. O perfil de segurança observado foi semelhante ao observado em adultos. Foi avaliada a segurança a longo prazo de dupilumab em 89 doentes adolescentes que foram inscritos num estudo de extensão aberto na asma moderada a grave (TRAVERSE). Neste estudo, os doentes foram acompanhados durante 96 semanas. O perfil de segurança de dupilumab no TRAVERSE foi consistente com o perfil de segurança observado nos estudos principais da asma até às 52 semanas de tratamento. Segurança a longo prazo. Dermatite atópica. O perfil de segurança de dupilumab + TCS (CHRONOS) em doentes adultos com dermatite atópica até à semana 52 foi consistente com o perfil de segurança observado na semana 16. A segurança a longo prazo de dupilumab foi avaliada num estudo de extensão aberto em doentes dos 6 aos 17 anos de idade com dermatite atópica moderada a grave (AD-1434). O perfil de segurança de dupilumab em doentes acompanhados até à semana 52 foi semelhante ao perfil de segurança observado na semana 16 nos estudos AD-1526 e AD-1652. O perfil de segurança a longo prazo de dupilumab observado em crianças e adolescentes foi consistente com o observado em adultos com dermatite atópica. Num estudo de fase 3, multicêntrico, de extensão aberta (OLE) (AD-1225), foi avaliada a segurança a longo prazo de doses repetidas de dupilumab em 2.677 adultos com DA moderada a grave expostos a uma dose semanal de 300 mg (99,7%), incluindo 347 que completaram, pelo menos, 148 semanas do estudo. O perfil de segurança a longo prazo observado neste estudo, até aos 3 anos, foi em geral consistente com o perfil de segurança de dupilumab observado em estudos controlados. Asma. O perfil de segurança do dupilumab no estudo de segurança a longo prazo de 96 semanas (TRAVERSE) foi consistente com o perfil de segurança observado nos estudos principais da asma até 52 semanas de tratamento. CRSwNP. O perfil de segurança de dupilumab em adultos com CRSwNP até à semana 52 foi consistente com o perfil de segurança observado na semana 24. Notificação de suspeitas de reações adversas A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício-risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao INFARMED, I.P.: Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (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 da revisão do texto:** Novembro de 2021. Medicamento Sujeito a Receita Médica restrita. Para mais informações contactar o representante local do Titular da Autorização de Introdução no Mercado.

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Skyrizi® (risancizumab)

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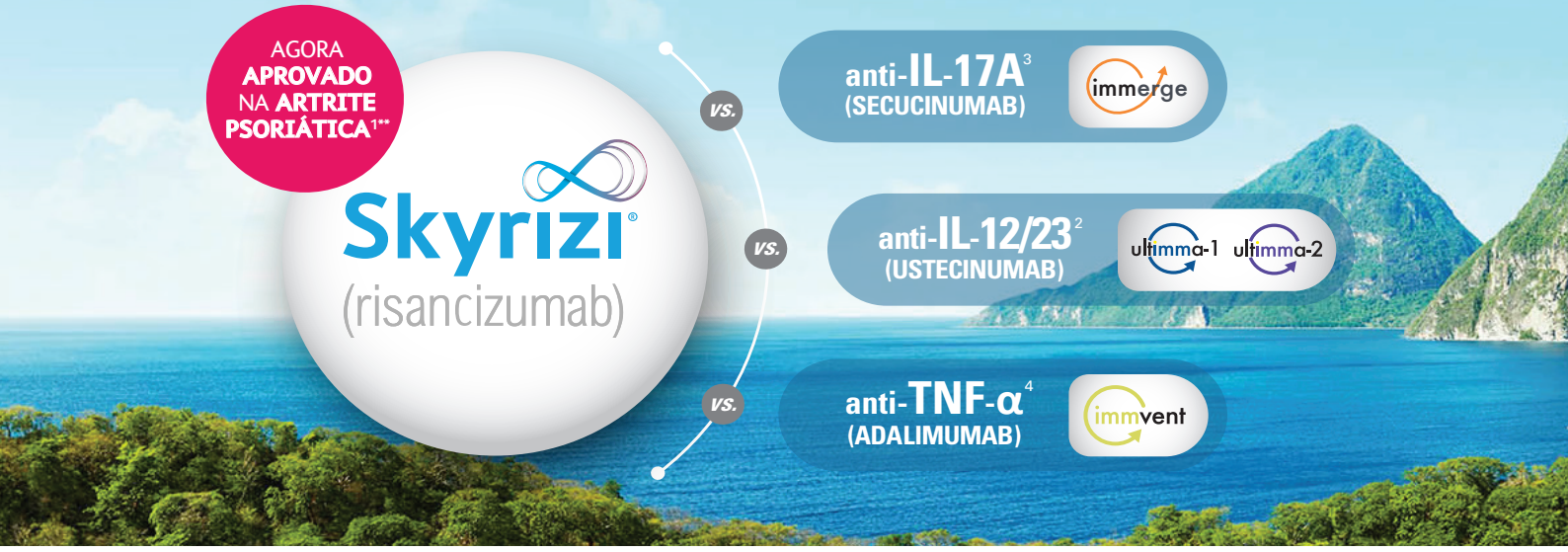
SKYRIZI® demonstrou SUPERIORIDADE* *versus* 3 CLASSES terapêuticas[1-4]

no tratamento de doentes adultos com psoríase em placas moderada a grave[1-4**]



* Ultimma 1 e 2 - PASI 90 à semana 52; Immerge - PASI 90 à semana 52; Immvent - PASI 90 à semana 44.

** Indicações terapêuticas: Psoríase em placas - Skyrizi é indicado para o tratamento da psoríase em placas, moderada a grave, em adultos que são candidatos a terapêutica sistémica. Artrite psoriática - Skyrizi, administrado em monoterapia ou em associação com metotrexato (MTX), é indicado para o tratamento da artrite psoriática ativa em adultos que tiveram uma resposta inadequada ou que demonstraram ser intolerantes a um ou mais fármacos antirreumáticos modificadores da doença (DMARDs).[1]

Referências: 1. RCM SKYRIZI®; **2.** Gordon KB, Strober B, Lebwohl M, *et al.* Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double blind, randomised, placebo controlled and ustekinumab controlled phase 3 trials. Lancet. 2018;392(10148):650-661. doi:10.1016/S0140-6736(18):31713-6.; **3.** Warren RB, *et al.* Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): Results from a phase 3, randomised, open-label, efficacy assessor-blinded clinical trial. British Journal of Dermatology. doi: 10.1111/BJD.19341; **4.** Reich K, Gooderham M, Thaçi D, *et al.* Risankizumab compared with adalimumab in patients with moderate to severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019;394(10198):576-586. doi: 10.1016/S0140-6736(19)30952-3.

NOME DO MEDICAMENTO E FORMA FARMACÊUTICA: Skyrizi 75 mg solução injetável em seringa pré-cheia; Skyrizi 150 mg solução injetável em caneta pré-cheia.**COMPOSIÇÃO QUALITATIVA E QUANTITATIVA:** Skyrizi 75 mg solução injetável em seringa pré-cheia: Cada seringa pré-cheia contém 75 mg de risancizumab em 0,83 ml de solução. Skyrizi 150 mg solução injetável em caneta pré-cheia: Cada caneta pré-cheia contém 150 mg de risancizumab em 1 ml de solução. **INDICAÇÕES TERAPÊUTICAS:** Psoríase – Skyrizi é indicado parao tratamento da psoríase em placas, moderada a grave, em adultos que são candidatos a terapêutica sistémica. Artrite psorática – Skyrizi, administrado em monoterapia ou em associação com metotrexato (MTX), é indicado para o tratamento da artrite psoriática ativa em adultos que tiveram uma resposta inadequada ou que demonstraram ser intolerantes a um ou mais fármacos antirreumáticos modificadores da doença (DMARDs). **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Skyrizi deverá ser utilizado sob a orientação e supervisão de um médico com experiência no diagnóstico e tratamento das condições para as quais Skyrizi está indicado. Posologia: A dose recomendada é de 150 mg administrada por injeção subcutânea na semana 0, semana 4 e posteriormente a cada 12 semanas (na forma de duas injeções de 75 mg com seringas pré-cheias ou de uma injeção de 150 mg com uma caneta pré-cheia). A descontinuação do tratamento deve ser considerada em doentes que não apresentem resposta após 16 semanas de tratamento. Alguns doentes com psoríase em placas com uma resposta inicial parcial podem apresentar melhorias com a continuação do tratamento para além das 16 semanas. Omissão de dose: Se não for administrada uma dose, esta deve ser administrada assim que possível. Posteriormente, a administração das doses deve ser retomada como normalmente agendado. Idosos (≥65 anos): Não é necessário ajuste posológico. A informação em indivíduos com idade ≥ 65 anos é limitada. Compromisso renal ou hepático: De uma forma geral, não é esperado que estas condições tenham qualquer impacto significativo na farmacocinética de anticorpos monoclonais e não são considerados necessários ajustes posológicos. População pediátrica: A segurança e eficácia de risancizumab em crianças e adolescentes com idades entre os 5 e os 18 anos não foram estabelecidas. Não existem dados disponíveis. Não existe utilização relevante de risancizumab em crianças com idade inferior a 6 anos para a indicação de psoríase em placas moderada a grave ou em crianças com idade inferior a 5 anos para a indicação de artrite psoriática. Doentes com excesso de peso: Não é necessário ajuste posológico. Modo de administração: Skyrizi é administrado por injeção subcutânea. A injeção deve ser administrada na coxa ou no abdómen. Os doentes não devem administrar a injeção em áreas onde a pele esteja sensível, com equimoses, eritematosa, endurecida, ou afetada por psoríase. Os doentes podem autoadministrar a injeção de Skyrizi após treino na técnica de injeção subcutânea. Os doentes devem ser instruídos a ler antes da administração as "Instruções de utilização" fornecidas no folheto informativo. A administração de Skyrizi na zona exterior superior do braço deve apenas ser realizada por um profissional de saúde ou prestador de cuidados. *Skyrizi 75 mg solução injetável em seringa pré-cheia:* Para a dose completa de 150 mg devem ser administradas duas seringas pré-cheias. As duas injeções devem ser administradas em diferentes zonas anatómicas. **CONTRAINDICAÇÕES:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes. Infeções ativas clinicamente relevantes (por exemplo, tuberculose ativa). **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** Rastreabilidade: De modo a melhorar a rastreabilidade dos medicamentos biológicos, o nome e número de lote do medicamento administrado devem ser rigorosamente registados. Infeções: Risancizumab pode aumentar o risco de infeção. Em doentes com uma infeção crónica, um historial de infeção recorrente, ou fatores de risco para infeção conhecidos, risancizumab deve ser utilizado com precaução. O tratamento com risancizumab não deve ser iniciado em doentes com qualquer infeção ativa clinicamente relevante até que a infeção se resolva ou seja adequadamente tratada. Os doentes tratados com risancizumab devem ser instruídos a procurar aconselhamento médico se surgirem sinais ou sintomas clinicamente relevantes de infeção crónica ou aguda. Se um doente desenvolver uma destas infeções ou não estiver a responder à terapêutica convencional para a infeção, o doente deve ser cuidadosamente monitorizado e não lhe deve ser administrado risancizumab até à resolução da infeção. Tuberculose: Antes de iniciar o tratamento com risancizumab, os doentes devem ser avaliados quanto a infeção por tuberculose (TB). Os doentes a receber risancizumab devem ser monitorizados quanto a sinais e sintomas de TB ativa. A terapêutica anti-TB deve ser considerada antes de iniciar risancizumab em doentes com história de TB latente ou ativa, nos quais não é possível confirmar um curso terapêutico adequado. Imunizações: Antes de iniciar a terapêutica com risancizumab, deve ser considerada a realização de todas as imunizações apropriadas de acordo com as atuais recomendações de imunização. Se um doente tiver recebido uma vacina viva (viral ou bacteriana), recomenda-se que aguarde pelo menos 4 semanas antes de iniciar o tratamento com risancizumab. Os doentes tratados com risancizumab não devem receber vacinas vivas durante o tratamento e durante, pelo menos, 21 semanas após o tratamento. Hipersensibilidade: Caso ocorra uma reação de hipersensibilidade grave, a administração de risancizumab deve ser descontinuada imediatamente e deve ser iniciada terapêutica apropriada. Excipientes com efeito conhecido: *Skyrizi 150 mg solução injetável em caneta pré-cheia*: Este medicamento contém menos do que 1 mmol (23 mg) de sódio por caneta pré-cheia ou seringa pré-cheia, ou seja, é praticamente "isento de sódio". *Skyrizi 75 mg solução injetável em seringa pré-cheia*: Este medicamento contém 68,0 mg de sorbitol por dose de 150 mg. Deve-se ter em consideração o efeito aditivo da administração concomitante de produtos contendo sorbitol (ou frutose) e a ingestão de sorbitol (ou frutose) na dieta. Este medicamento contém menos do que 1 mmol (23 mg) de sódio por dose de 150 mg, ou seja, é praticamente "isento de sódio". **INTERAÇÕES MEDICAMENTOSAS E OUTRAS FORMAS DE INTERAÇÃO:** Não é esperado que risancizumab seja metabolizado por enzimas hepáticas ou eliminação renal. Não são esperadas interações entre risancizumab e inibidores, indutores, ou substratos de enzimas metabolizadoras de medicamentos, e não é necessário qualquer ajuste posológico. **EFEITOS INDESEJÁVEIS:** As reações adversas mais frequentemente notificadas foram infeções do trato respiratório superior. Reações adversas medicamentosas notificadas em doentes tratados com risancizumab: muito frequentes – infeções do trato respiratório superior; frequentes – infeções por tinha, cefaleia, prurido, fadiga, reações no local de injeção; pouco frequentes – foliculite. Consultar o RCM para mais informações relativamente a efeitos indesejáveis.

▼Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Quaisquer suspeitas de reações adversas a Skyrizi devem ser notificadas à AbbVie, Lda., via e-mail para pt.abbvie.farmacovigilancia@abbvie.com ou telefone para +351 211 908 400 e/ou ao INFARMED. I.P., através do sistema nacional de notificação, via e-mail para farmacovigilancia@infarmed.pt ou telefone para +351 217 987 373.

Revisão do texto das IECRCM: novembro 2021 (PsA)

Medicamento de receita médica restrita, de utilização reservada a certos meios especializados.

Skyrizi está comparticipado no tratamento de doentes adultos com psoríase em placas moderada a grave, elegíveis para terapêutica sistémica, em que o tratamento sistémico não biológico não é eficaz, não é tolerado ou está contraindicado, ao abrigo da Portaria 48/2016 de 22 de Março. A artrite psoriática não está ainda comparticipada. Consultar o RCM antes de prescrever e sempre que necessite de informações complementares. Para mais informações deverá contactar o representante local do titular da autorização de introdução no mercado**.** Representante local do titular da AIM: AbbVie, Lda. Estrada de Alfragide, 67 - Alfrapark - Edifício D - 2610-008 Amadora, Portugal. Tel.: 211908400. Fax: 211908403. CRC Amadora. NIF 510 229 050 – Capital Social €4.000.000.

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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 ×40). See article by Freitas et al. in this issue.

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 sistémica 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 pro-fármacos (como capecitabina, tegafur) e associações de medicamentos contendo estas substâncias ativas ou outras fluoropirimidinas. Terapia antifúngica com flucitosina: brivudina está contraindicada em doentes que receberam recentemente ou estão a receber terapia antifúngica com flucitosina, 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.

ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:

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 flucitosina) (um pró-fármaco do 5-fluorouracilo). A interação entre a brivudina e fluoropirimidinas (por exemplo, capecitabina, 5-FU, tegafur, flucitosina, 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, flucitosina, etc.), No caso de administração acidental 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 sistémica infeções e desidratação. Centros especiais de intoxicação (se disponíveis) devem ser contatados o mais rápido possível para encontrar uma ação apropriada contra a toxicidade da fluoropirimidinas. 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 crónicas como hepatite. Dados pós-comercialização indicam que estender o tratamento pela duração recomendada de 7 dias aumenta o risco de 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 glucose-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 nucleósidos antivíricos 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: granulocitopénia, eosinofilia, anemia, linfocitose, monocitose. Raros: trombocitopenia. Doenças do sistema imunitário Pouco frequentes: reações alérgicas / hipersensibilidade (edema periférico e edema de língua, lábio, laringe pálpebra e na face, prurido, erupção cutânea, aumento da sudação, 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 Síncope, distúrbio do equilíbrio, hiperatividade psicomotora Afeções do ouvido e do labirinto Raras Dor de ouvidos Afeções gastrintestinais Frequentes: náuseas. Pouco frequentes: dispepsia, vómitos, dor abdominal, diarreia, flatulência, obstipação. Afeções hepatobiliares Pouco frequentes: fígado gordo, 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 musculosqueléticas 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

Bridic 1
Brivudina

Comodidade posológica

APENAS 1 POR DIA X 7 DIAS [1]

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, vómito, 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

Informações revistas em Fevereiro de 2021. Medicamento sujeito a receita médica. Escalão B (Regime Geral 69%). Refª. 04/2021

A. MENARINI PORTUGAL

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Rua dos Malhões nº 1, 2770-071 Paço de Arcos
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MANCHAS E RUGAS

5% NIACINAMIDA + 8% COMPLEXO PEELING + VITAMINA CG

SOLUÇÃO DERMOCOSMÉTICA ALTAMENTE CONCENTRADA PARA A PREVENÇÃO E CORREÇÃO DAS MANCHAS

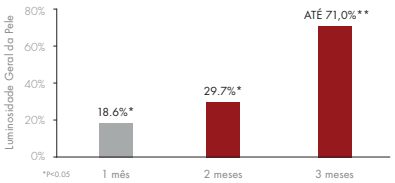
EFICÁCIA CLÍNICA

1 REDUZ AS MANCHAS
2 UNIFORMIZA A TEZ
3 MELHORA A APARÊNCIA GLOBAL DA PELE

REDUÇÃO DE MANCHAS

EFICÁCIA MÉDIA DE **29,7%** NA REDUÇÃO DAS MANCHAS

ITA° SOBRE A ÁREA DAS MANCHAS



*52 mulheres caucasianas, fotótipo I a IV, 50% pele sensível. Uso de Liftactiv Sérum B3 2x dia, 2 meses + Hidratante standard. **em 33% dos indivíduos estudados.

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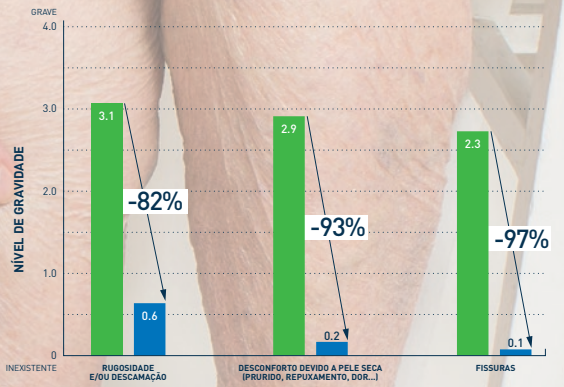
ESTUDO NOVO CLÍNICO

PODE UMA
ROTINA COM CERAMIDAS
MELHORAR CLINICAMENTE A XEROSE E A QUALIDADE DE VIDA EM DOENTES IDOSOS COM MEDICAÇÃO CONCOMITANTE?

AVALIAÇÃO DERMATOLÓGICA

Até **97% de MELHORIA** dos sinais e sintomas de pele seca em apenas 4 semanas



*Hydrating Cleanser + Moisturising Cream
Protocolo: Foi realizado um estudo clínico de 4 semanas, num único centro, em 30 mulheres e homens com mais de 70 anos, com evidências de xerose e/ou descamação, com uma doença sistémica e/ou sob medicação concomitante com o efeito secundário de xerose. Hydrating Cleanser foi utilizado pelo menos uma vez por dia no corpo e Moisturising Cream foi aplicado duas vezes por dia no corpo. A eficácia foi avaliada por classificação clínica no início do estudo e na semana 4. Foram tiradas fotografias e realizadas auto-avaliações no início do estudo e na semana 4.

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CICAPLAST BAUME B5+

INOVAÇÃO

TRIBIOMA COMPLEXO PREBIÓTICO REEQUILIBRA O MICROBIOMA

PANTENOL 5% APAZIGUA A PELE

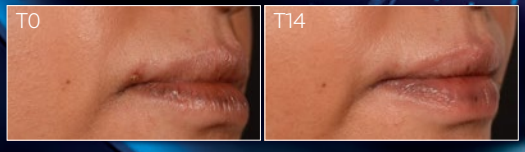
MADECASSOSIDE ACELERA O PROCESSO DE REPARAÇÃO

TESTADO EM **~20.000** DOENTES DESDE **A PRIMEIRA SEMANA ATÉ AOS 97 ANOS** DE IDADE

21 INDICAÇÕES TODOS OS FOTOTIPOS

QUEIMADURAS SUPERFICIAIS DE PRIMEIRO GRAU[2]

QUEILITE[2]



2º DIA[1]

98%

DOS DOENTES TIVERAM UMA MELHORIA GLOBAL

21º DIA[1]

74%

DOS DOENTES RECUPERARAM COMPLETAMENTE

1. Avaliação em 23 doentes com dermatite irritativa com fissuras, eczema xerótico e placas xeróticas.
2. Avaliação em 54 doentes com irritações cutâneas.

LA ROCHE-POSAY. A EXIGÊNCIA DERMATOLÓGICA.

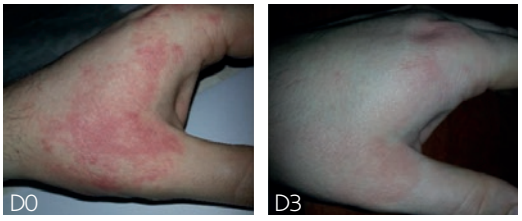
LA ROCHE POSAY
LABORATOIRE DERMATOLOGIQUE

DISPOSITIVO MÉDICO

LIPIKAR **ECZEMA MED**

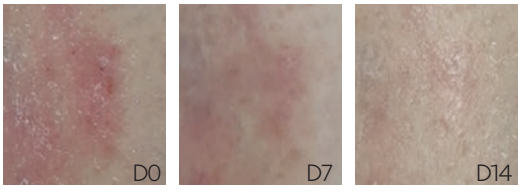
[ENDOBIOMA]

EFICAZ CONTRA
OS SINTOMAS DE ECZEMA
A PARTIR DO 3º DIA*



MELHORA OS SINTOMAS
EM 3 DIAS:

-26% PRURIDO
-33% SENSAÇÃO DE FORMIGUEIRO



REDUÇÃO DO SCORAD:
-43% APÓS 7 DIAS
-68% APÓS 14 DIAS

PARA BEBÉS, CRIANÇAS E ADULTOS
TAMBÉM PARA ZONAS MAIS SENSÍVEIS
COMO AS PÁLPEBRAS
EXCELENTE TOLERÂNCIA

*Estudo clínico em 43 doentes

LA ROCHE-POSAY. A EXIGÊNCIA DERMATOLÓGICA.

IECRCM161221

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 Ovário 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 ou intolerantes ao tratamento com um ou mais fármacos antirreumatismais 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 pré-cheia 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 tinha (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, dispneia 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 (23 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 quecorresponde 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
	Raras	Anafilaxia
Doenças respiratórias, torácicas e do mediastino	Frequentes	Dor orofaríngea
Doenças gastrointestinais	Frequentes	Náusea
	Pouco frequentes	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[a]

[a] *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 baixos 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 na psoríase em placas, 9% dos doentes tratados com Taltz desenvolveram neutropenia. Na maioria dos casos, a contagem de neutrófilos foi ≥ 1.000 células/mm^3. 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/mm^3. 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/mm^3 a ≥75.000 plaquetas/mm^3. 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 nos estudos 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, à 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/submissaoram (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/. Medicamento sujeito a receita medica restrita. Para mais informações devera contatar o representante local do Titular da Autorização de Introdução no Mercado.

Referências: 1. RCM Taltz®.

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Port J Dermatol and Venereol. **ORIGINAL ARTICLE**

Treatment of chronic urticaria with omalizumab: the experience of Hospital de Braga

Tratamento de urticária crónica com omalizumab: a experiência do Hospital de Braga

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Abstract

Introduction: Omalizumab is approved for the treatment of severe chronic spontaneous urticaria (CSU), unresponsive to quadruple doses of nonsedative H1 antihistamine. Few data are available to help predict the response to omalizumab in the Portuguese population. **Objective:** Characterize the population of CU patients treated with omalizumab in Hospital de Braga and identify variables that help predict a better response to omalizumab. **Methods:** Retrospective chart-review study of CU patients treated with omalizumab in Hospital de Braga. Statistical analysis was performed using the chi-square, odds ratio analysis and generalized linear models. **Results:** 21 patients were included (three men and 18 women). 16 patients had CSU, two had solar urticaria, two cholinergic urticaria, and one cold urticaria. They all had at least 6 months of treatment with omalizumab. Prior to omalizumab, they all had been treated with quadruple doses of nonsedating H1 antihistamines. Using generalized linear models, patients showed a significant reduction of the UAS and UAS7 scores. Women and patients with intermediate levels of immunoglobulin (Ig)—IgE presented a bigger reduction. Women had higher total serum IgE. **Conclusion:** The female gender and patients with intermediate levels of IgE had a better response to omalizumab. In this study, the female gender seems to have higher total serum IgE.

Keywords: Antihistamines. Chronic urticaria. IgE levels. Omalizumab. Urticaria.

Resumo

Introdução: O omalizumab está aprovado para o tratamento de urticária crónica espontânea que resistente a terapêutica quádrupla com anti-histamínicos. Há pouca informação disponível que ajude a prever a resposta ao omalizumab na população portuguesa. **Objetivos:** Caracterizar a população de doentes com urticária crónica tratados com omalizumab no Hospital de Braga e identificar variáveis que ajudem a prever uma melhor resposta ao omalizumab. **Métodos:** Foi efetuado um estudo retrospetivo dos doentes com urticária crónica tratados com omalizumab no Hospital de Braga. Realizou-se análise estatística com estatística descritiva, *chi-square*, análise de risco e modelo linear generalizado. **Resultados:** Foram incluídos 21 doentes (3 homens e 18 mulheres). 16 doentes apresentavam urticária crónica espontânea, 2 tinham urticária solar, 2 urticária colinérgica e 1 urticária ao frio. Todos estavam a ser tratados com omalizumab há pelo menos 6 meses. Antes do

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omalizumab todos tinham sido tratados com terapêutica anti-histamínica quádrupla. Modelos lineares generalizados mostraram que os doentes apresentaram uma redução significativa dos scores Urticaria Activity Score (UAS) e UAS7. Estas reduções foram mais proeminentes nos doentes do sexo feminino e em doentes com níveis intermédios de IgE. As mulheres apresentaram níveis de IgE mais elevados. **Conclusão:** O género feminino e doentes com níveis intermédios de IgE apresentaram melhor resposta ao omalizumab. Neste estudo o género feminino parece estar associado a níveis de IgE mais elevados.

***Palavras-chave*:** Anti-histamínico. Urticária crónica. IgE. Omalizumab. Urticária.

Introduction

Urticaria is a common disease presenting with wheals and/or angioedema[1].

The classification of urticaria is mainly based on clinical criteria: acute and CU, whether the lesions appear over a period of up to 6 weeks or over > 6 weeks, respectively. The acute form affects 20% of the general population and CU up to 5%[2].

Chronic urticaria comprises both CSU and chronic inducible urticaria, which includes physical and non-physical urticaria.

In CU patients, mental health and physical impairment can be comparable to patients with moderate and severe psoriasis[3]. For the assessment of disease activity, quality of life, and the impact on daily activities, a number of detailed questionnaires have been developed. The urticaria activity score 7 (UAS7) assesses the number of wheals and itch intensity on seven consecutive days and was shown to correlate with the impact on quality of life, sleep and daily activities[4,5].

Currently, nonsedating antihistamines and omalizumab, an anti-immunoglobulin E antibody, are recommended for the therapy of CU. Omalizumab is approved for the treatment of severe CSU, unresponsive to quadruple dose of nonsedative H1 antihistamine[6]. Few data are available to help predict the response to omalizumab in the Portuguese population.

The purpose of this case series is to characterize the population of patients with CU that are being treated with omalizumab in Hospital de Braga and try to identify variables that may help predict a better response to omalizumab.

Methods

A retrospective chart review study of patients with CU being treated with omalizumab in the Immunoallergology and Dermatology Departments of Hospital de Braga between January and December 2020.

Patients were characterized according to demographic and clinical data, such as age, gender, presence of atopic comorbidities, age of onset and duration of CU, age at the beginning of omalizumab, previous treatments, initial omalizumab dose, total serum IgE, and results of other complementary studies, including the autologous serum test (AST) and antithyroid antibodies (ATA).

Clinical response to omalizumab was evaluated with the UAS and UAS7, validated in the Portuguese language, and calculated before and during treatment. Patients started omalizumab associated with their previous medications, which were later discontinued according to their clinical improvement.

Patients were characterized according to their response to omalizumab as:

- Complete responders–need of antihistamines in SOS besides omalizumab to keep UAS ≤ 6;
- Partial responders–need of daily medication besides omalizumab to keep UAS ≤ 6, but showed a clinical improvement since the start of omalizumab
- Nonresponders–patients that showed no improvement after 6 months of omalizumab treatment.

The adverse reactions were monitored by the nursing staff after each administration.

Statistical analysis and descriptive statistics of the data were performed using the Statistical Package for the Social Sciences software version 23.0 (IBM Corporation), using the chi-square, odds ratio analysis, and generalized linear models. A p-value < 0.05 was considered statistically significant.

Results

In this study, 21 patients with CU were included (18 women and three men). The descriptive statistics are shown in tables 1 and 2. They all started omalizumab at the dose of 300 mg every 4 weeks.

A total of 16 patients had CSU; two had solar urticaria, two cholinergic urticaria and one cold urticaria.

About six patients had atopic comorbidities (n = 6 and 28.6%), namely atopic dermatitis, allergic rhinitis, asthma, and allergic eczema.

Table 1. Descriptive statistics of CU patients treated with omalizumab in Hospital de Braga

Characteristics	Mean ± standard deviation	Median (min and max)
Age at onset of urticaria (years)	37 ± 12	33 (17, 62)
Age at onset of omalizumab (years)	41 ± 12	39 (22 and 63)
Time between urticaria onset and omalizumab treatment (years)	4 ± 4	2 (0.5 and 12)
Duration of omalizumab treatment (months)	20 ± 13	18 (6 and 60)
Total serum IgE (kU/L)	335.9 ± 319.5	326.5 (3 and 1187)
Initial UAS	5.19 ± 0.87	5 (3 and 6)
Final UAS	0.95 ± 1.28	1 (0 and 4)
Initial UAS7	19.71 ± 5.64	20 (9 and 38)
Final UAS7	± 2.67	0 (0 and 21)

A total of 14 patients had their total serum IgE measured before the start of treatment: three patients had IgE > 500 kU/L, seven between 100 and 500 kU/L and four under 100 kU/L. Only one patient underwent an AST guided by the patient's clinical history, and it was negative. They all had negative antithyroid antibodies.

Prior to omalizumab, they all had been treated with quadruple doses of nonsedating H1 antihistamines, 12 with systemic corticotherapy, 10 with cyclosporine, eight with montelukast, one with hydroxychloroquine, one with intravenous immunoglobulin, one with oxybutynin, and one with ultraviolet B (UVB) phototherapy. This last patient also had allergic eczema.

Currently, 19 patients are being treated with omalizumab (medium duration of treatment: 19.9 months). One patient discontinued omalizumab for pregnancy reasons.

There were 11 complete responders in this study, 10 partial responders (two needed dose increase to 450 mg every 4 weeks) and one nonresponder. The nonresponder is a 40-year-old female patient with CSU, no atopic comorbidities and low serum IgE, previously treated with montelukast and cyclosporine. This patient was switched to dupilumab since recent knowledge shows dupilumab may be a promising novel treatment option for patients with CU and low IgE levels.

Patients well controlled with omalizumab have started to increase the time intervals between each dose of omalizumab, but none has yet stopped this treatment.

There were no adverse reactions after the administration of omalizumab.

Statistical analysis

The urticaria activity was determined with the assessment of the UAS score before the start of omalizumab and 6 months after starting treatment.

The results are shown in tables 3 and 4.

Using the paired samples *t*-test, there was a significant difference between the initial and final scores for UAS and UAS7. The patients showed a reduction of 4.2 points on the UAS score ($p < 0.001$) and of 17.0 points on the UAS7 ($p < 0.001$), in comparison to the scores before the start of treatment.

According to gender, women showed a UAS score reduction of 4.3 points and men of 3.7 points ($p < 0.001$). Considering UAS7, women showed a score reduction of 17.3 points and men of 15.3 points.

When the results were evaluated according to the total serum IgE of each patient, patients with IgE < 100 kU/L showed a reduction of 4.0 points and 16.3 points on the UAS and UAS7 scores, respectively, patients with IgE 100-500 kU/L showed a reduction of 4.7 and 19.8 points on the UAS and UAS7 scores respectively, and patients with IgE > 500 kU/L showed a reduction of 3.3 points on the UAS and of 15.0 points on the UAS7 score.

We searched for an association between gender and the total serum IgE. The chi-square test showed an association ($p < 0.05$), women presented with more elevated values of IgE.

Discussion

Omalizumab is approved as an add-on therapy for CSU[7]. Few studies have tried to find predictor factors for omalizumab response in CSU in the Portuguese population.

To be able to predict the response to omalizumab is important for clinical practice since it is an expensive therapy, and not all patients respond to it.

About 17-48% of patients with CSU do not have a complete or significant response to omalizumab[8-10]. In this study, 52% didn't have a complete response to omalizumab. So, it seems important to try and find ways to select those patients that will benefit more from omalizumab.

One study showed that female patients seem to have a faster and better response to omalizumab, which is in line with our results. It also concluded that patients

Table 2. Descriptive statistics of the 21 CU patients treated with omalizumab in Hospital de Braga

Patient	Sex	CU type	Age of urticaria onset	Age at the beginning of omalizumab	Time between urticaria onset and omalizumab treatment (years)	Duration of omalizumab treatment at 30th November 2020 (months)	Atopic comorbidities	Previous medications	Total serum IgE	AST	ATA
1	m	C	17	26	9	12	AD	anti-H, CyA, and montelucaste	504	ND	ND
2	f	CSU	42	52	10	60	-	anti-H, CCT, and IVIg	34	ND	ND
3	f	CSU	33	35	2	12	AD and allergic rhinitis	Anti-H, CyA, and CCT	487	ND	ND
4	f	CSU	42	45	3	24	Allergic rhinitis	Anti-H, CyA, CCT	ND	ND	ND
5	f	CSU	62	63	1	18	-	Anti-H, CyA, and montelucaste	ND	ND	neg
6	f	CSU	42	42	0.5	18	-	Anti-H, CyA, and CCT	ND	ND	neg
7	f	CSU	25	39	11	12	-	Anti-H and CCT	291	ND	neg
8	f	CSU	33	34	2	18	Asthma	Anti-H and montelucaste	39	ND	neg
9	f	CSU	29	29	0.5	24	-	Anti-H	3	ND	neg
10	f	CSU	33	34	1	16	-	Anti-H, CCT, and montelucaste	ND	ND	ND
11	f	CSU	41	47	6	24	-	Anti-H, CyA, and CCT	172	ND	neg
12	f	CSU	25	37	12	24	-	Anti-H, CyA, and montelucaste	3	neg	neg
13	f	CSU	25	28	3	12	-	Anti-H and CCT	122	ND	neg
14	f	CSU	50	54	4	48	-	Anti-H, CCT, and montelucaste	401	ND	neg
15	f	CSU	38	41	3	12	-	Anti-H, CCT, and montelucaste	ND	ND	neg
16	m	CSU	37	39	1.5	18	-	Anti-H, CyA, and HCQ	38	ND	neg
17	f	S	28	31	3	6	-	Anti-H and CyA	362	ND	neg
18	f	CSU	60	62	2	18	-	Anti-H and CCT	463	ND	neg
19	m	Cold	30	31	1	18	Asthma and allergic rhinitis	Anti-H and montelucaste	1187	ND	ND
20	f	C	58	60	2	6	Allergic eczema	Anti-H, CyA, and UVB	606	ND	neg
21	f	S	21	22	1	18	-	Anti-H, CyA, CCT, and oxybutynin	ND	ND	neg
Patient	Sex	Age at the beginning of urticaria	Age at the beginning of omalizumab	Time between the beginning of urticaria and the beginning of omalizumab (years)	Duration of omalizumab treatment at 30th November 2020 (months)	Atopic comorbidities	Previous medications	Total serum IgE	AST	ATA	
1	m	17	26	9	12	AD	Anti-H, CyA, and montelucaste	504	-	-	
2	f	42	52	10	60	-	Anti-H, CCT, and IVIg	34	-		

(continues)

Table 2. Descriptive statistics of the 21 CU patients treated with omalizumab in Hospital de Braga *(continued)*

Patient	Sex	CU type	Age of urticaria onset	Age at the beginning of omalizumab	Time between urticaria onset and omalizumab treatment (years)	Duration of omalizumab treatment at 30th November 2020 (months)	Atopic comorbidities	Previous medications	Total serum IgE	AST	ATA
3	f	33	35	2	12	AD, allergic rhinitis	Anti-H, CyA, CCT	487	-	-	
4	f	42	45	3	24	Allergic rhinitis	Anti-H, CyA, CCT	-	-	-	
5	f	62	63	1	18	-	Anti-H, CyA, and montelucaste	-	-	neg	
6	f	42	42	0.5	18	-	Anti-H, CyA, and CCT	-	-	neg	
7	f	25	39	11	12	-	Anti-H, CCT	291	-	neg	
8	f	33	34	2	18Asthma		Anti-H and montelucaste	39	-	neg	
9	f	29	29	0.5	24	-	Anti-H	3	-	neg	
10	f	33	34	1	16	-	Anti-H, CCT, and montelucaste	-	-	-	
11	f	41	47	6	24	-	Anti-H, CyA, and CCT	172	-	neg	
12	f	25	37	12	24	-	Anti-H and montelucaste	3	neg	neg	
13	f	25	28	3	12	-	Anti-H and CCT	122	-	neg	
14	f	50	54	4	48	-	Anti-H, CCT, and montelucaste	401	-	neg	
15	f	38	41	3	12	-	Anti-H, CCT, and montelucaste	-	-	neg	
16	m	37	39	1.5	18	-	Anti-H, CyA, and HCQ	38	-	neg	
17	f	28	31	3	6	-	Anti-H and CyA	362	-	neg	
18	f	60	62	2	18	-	Anti-H and CCT	463	-	neg	
19	m	30	31	1	18	Asthma, allergic rhinitis	Anti-H and montelucaste	1187	-	-	
20	f	58	60	2	6	Allergic eczema	Anti-H, CyA, and UVB	606	-	neg	
21	f	21	22	1	18	-	Anti-H, CyA, CCT, and oxybutynin	-	-	neg	

AST: autologous serum test; ATA: antithyroid antibodies; AD: atopic dermatitis; anti-H: quadruple dose nonsedating H1 antihistamines; C: cholinergic urticaria; Cold: cold urticaria; CSU: chronic spontaneous urticaria; CyA: cyclosporine; CCT: corticotherapy; IVIg: intravenous immunoglobulin; HCQ: hydroxychloroquine; ND: not done; S: solar urticaria; UVB: Ultraviolet B phototherapy.

Table 3. Urticaria activity score and UAS7 reduction in each group of patients according to gender and total serum IgE levels

Variables	UAS reduction	UAS7 reduction
All patients	4.2 ($p < 0.001$)	17.0 ($p < 0.001$)
Female	4.3 ($p < 0.001$)	17.3 ($p < 0.001$)
Male	3.7 ($p < 0.001$)	15.3
IgE < 100 kU/L	4.0	16.3 ($p < 0.001$)
IgE 100-500 kU/L	4.7 ($p < 0.001$)	19.8 ($p < 0.001$)
IgE > 500 kU/L	3.3 ($p < 0.001$)	15.0

Table 4. Type of response to omalizumab

Response to omalizumab	Number of patients
Total response	11
Partial response	9
No response	1

with more elevated total serum IgE levels had a better response to omalizumab. However, in this study, patients with intermediate levels of total serum IgE presented a bigger improvement[11]. This could have also happened because there were only 3 patients with total serum IgE > 500 in this study.

One Portuguese study applied generalized linear models to evaluate the progression of the UAS score in response to omalizumab. They showed a medium reduction of the UAS score of 16% and of UAS7 of 20% per monthly administration of omalizumab. These reductions were also more prominent in female patients and in patients with higher total serum IgE levels[12].

There was an association between the female gender and higher levels of total serum IgE, and this could be a possible explanation for the better response to omalizumab in the female group.

Most patients presented with a total response to omalizumab (n = 11 and 52.4%), some have already started interval prolongation, but none have yet stopped treatment. The nonresponder patient was switched to dupilumab and has shown improvement.

Some limitations of this study are the fact that it's a retrospective study, the global sample is small, in particular the male gender. Also, the scores used are subjective; the literature shows women tend to have initial higher scores than men.

Not all patients had every laboratory study, like total serum IgE or antithyroid antibodies, and there are other clinical parameters that can affect the response to treatment and weren't evaluated, like body weight, eosinopenia, and others.

Conclusion

The female gender and patients with intermediate levels of IgE had a better response to omalizumab in this study. The female gender seems to have higher total serum IgE, and maybe that is the reason they had a better response to omalizumab. This study's population is small to extrapolate conclusions to the general Portuguese population.

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.

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ORIGINAL ARTICLE

Positive drug patch tests and the acute cutaneous adverse drug reaction share many histopathologic features

As caracteristicas histopatológicoas dos testes epicutâneos positivos com fármacos são semelhantes às das reacções cutâneas adversas medicamentosas que motivaram os testes

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Abstract

Patch testing (PT) has been used to evaluate the culprit drug and cross-reactive chemicals in non-immediate cutaneous adverse drug reactions (CADR), but histopathology of patch tests is seldom performed. With the objective of characterizing the patterns of positive drugs patch tests in correlation with the acute skin reaction, we performed skin biopsies in 16 patients with different CADR, five cases of acute generalized exanthematous pustulosis (AGEP), six cases of maculopapular exanthema (MPE), four cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and one case of toxic epidermal necrolysis (TEN). Particular macroscopic features of drug patch tests included pustules, particularly in AGEP, and epidermal necrosis in TEN and on histopathology, we highlight the occurrence of subcorneal spongiform pustules in AGEP, full-thickness epidermal necrolysis in the case of TEN and vacuolization of basal cells, lymphocyte exocytosis with occasional necrotic keratinocytes and a perivascular and interstitial lymphocyte infiltrate both in DRESS and MPE, although less intense in the latter. Similarities between the acute eruption and the patch test suggest the patch test can be considered a form of localized drug provocation test that can be used to further investigate the pathophysiology of CADR.

Keywords: Acute generalized exanthematous pustulosis. Drug reaction with eosinophilia and systemic symptoms. Histopathology. Non-immediate drug eruptions. Patch testing. Toxic epidermal necrolysis.

Resumo

O teste epicutâneo tem sido utilizado para o diagnóstico etiológico das reações cutâneas adversas a medicamentos (CADR) mediadas por reações de hipersensibilidade retardada, mas raramente é estudado o seu aspeto histopatológico. Com o objetivo de caracterizar os padrões histopatológicos de testes epicutâneos positivos a fármacos sistémicos e correlacioná-los com a reação aguda, efetuámos biópsias de testes epicutâneos positivos em 16 doentes com diferentes CADR, 5 casos de pustulose exantemática aguda generalizada (AGEP), 6 casos de exantema maculopapular (MPE), 4 casos de DRESS (Drug reaction with eosinophilia and systemic symptoms) e 1 de necrólise epidérmica tóxica (TEN). Encontrámos aspetos

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particulares dos testes tanto na avaliação macroscópica como microscópica. Da primeira destacamos as pústulas nos casos de AGEP e a necrose epidérmica no caso de TEN e na histopatologia salientamos a existência de pústulas espongiformes subcórneas na AGEP, necrose de toda a espessura da epiderme no caso de TEN e vacuolização das células basais, exocitose de linfócitos com ceratinócitos necróticos ocasionais e um infiltrado linfocitário perivascular e intersticial tanto nos testes de DRESS como de MPE, com alterações de menor intensidade no MPE. Estas semelhanças entre a reação aguda e o teste epicutâneo permitem considerar este teste como um teste de provocação localizado que, além do diagnóstico etiológico, pode também ser utilizado para estudar aspetos da fisiopatologia da CADR.

Palavras-chave: Exantema medicamentoso. Patch test. Teste epicutâneo. Histopatologia. AGEP. TEN. DRESS

Introduction

Patch testing is used mainly in the study of allergic contact dermatitis (ACD), but recently PT has also been used more regularly in the study of non-immediate T cell-mediated CADR[1-3].

Actually, PT was first used in the study of a drug reaction, a generalized acute eczematous dermatitis, after a mercury injection for treating syphilis. Originally called "Funktionelle Hautprufung," this technique was developed at the University of Breslau in the 1890s by Joseph, now considered the "father" of patch testing[4]. In the 1970s, Felix et al. first published the value of patch testing in drug eruptions[5]. After the 1990s, isolated cases and smaller or larger studies reported that PT could confirm the responsible drug in CADR[6-10], mainly from carbamazepine[11-13] and penicillin[14,15], and in 2001 the European Society of Contact Dermatitis (ESCD) guidelines for performing skin tests in drug eruptions were pusblished[16].

PT is a specific and safe diagnostic test if performed according to the recommendations, with very exceptional cases of immediate reactions or CADR reactivation[17,18], but its sensitivity is lower than in ACD and depends both on the pattern of CADR and the culprit drug. Patch tests (PTs) have always been negative with allopurinol and its active metabolite, oxypurinol[19,20], but positive in virtually all cases of abacavir hypersensitivity[21-24], in 60-75% of CADR from carbamazepine[20] and in > 30% from aminopenicillins,[25-28] pristinamycin[29], clindamycin[30,31], and tetrazepam[18,32-34]. PTs are more frequently positive in MPE, DRESS, symmetrical drug-related intertriginous and flexural exanthema, AGEP and fixed drug eruption[20,35], whereas they occur in < 10% in Stevens-Johnson syndrome/TEN (SJS/TEN)[9,36]. PT can also confirm cross-reactivity between drugs, namely between piroxicam and tenoxicam or between different piperazine antihistamines,[37,38] or absence of cross-reactivity, as for instance, between etoricoxib and celecoxib[39] or between meropenem and imipenem[40]. Moreover, PT reactivity can be evoked many years after the acute reaction[41].

As in ACD, apart from confirming the etiologic agent, the study of cells infiltrating the skin in PTs has been used to study pathophysiologic mechanisms involved in delayed CADR[9,22,34]. Drug-specific T cells from a positive patch, some with similar phenotypic characteristics as those involved in the acute CADR, have been isolated from PTs, and T cell lines and clones were established to study in vitro reactivity with the responsible drugs.[42,43]

Objectives

The objective of the present work was to characterize positive PTs to drugs in different patterns of non-immediate CADR, both on their macroscopic morphology and, particularly, on histopathology, in order to understand how PTs can reproduce the features of the different patterns of CADR. This might reinforce their potential use to study pathophysiologic mechanisms involved in the effector phase of immune-mediated CADRs.

Methods

Between 2008 and 2013, at the Department of Dermatology of Centro Hospitalar e Universitário de Coimbra, we performed skin biopsies in patients with positive drug PTs performed according to the ESCD recommendations in non-immediate CADR.[16] Only non-pregnant patients older than 18 years, observed during the acute phase at the Department of Dermatology with a non-immediate CADR clearly classified according to the regularly defined phenotypes[44,45] were selected. All patients gave their written informed consent for photographing PTs and performing skin biopsies at the patch test site.

This study was approved by the ethics committee of the Faculty of Medicine of the University of Coimbra in 2008, within a broader study for a doctoral thesis for the characterization of non-immediate drug eruptions[46].

Patch testing methods and materials

Patients were patch tested at least 6 weeks after the complete resolution of the drug eruption and no longer

than 6 months thereafter. PT was performed with the suspected drug and chemically related substances or drugs belonging to similar pharmacological groups, mostly with drug allergens from Chemotechnique Diagnostics, Vellinge, Sweden or Bial-Aristégui, Spain, usually at 1-10% in petrolatum. When not commercially available, the powder of the drug with >95% purity, kindly supplied by the pharmaceutical industry, was prepared in our department at 1-20% concentration in petrolatum. When we had no access to the pure product, we used the powder from i.v. preparations or capsules or, in its absence, from crushed tablets. The powder was freshly diluted in petrolatum in order to have a concentration of the active drug at 10% in the final preparation, or when there was a too-low amount of the active drug in the commercial preparation, the whole powder was prepared at 30% in petrolatum.

Drug allergens were applied for 48 h on the back, using 8 mm aluminum Finn chambers® mounted on Scanpor® tape, Epitest Ld Oy or IQ Ultra® square polyethylene foam chambers attached to a hypoallergenic tape, Chemotechnique Diagnostic, Vellinge, Sweden, and covered with Mefix® tape or analog.

Readings were performed twice, between day 2 (D2) and D7, usually with a common reading on D3, and rated according to ICDRG (International Contact Dermatitis Research Group) guidelines and scoring system (-negative, IR irritant, '?' doubtful, and positive 1+, 2+ or 3+). A particular emphasis was put on the description of morphological aspects of the skin reaction, other than the erythema, infiltration, papules, and vesicles regularly observed in patch tests from contact allergens. Photographs of the positive reactions were obtained.

Skin biopsy collection and histopathology evaluation

After the patient's written informed consent, on D3 or D4, a 4 mm skin punch biopsy was performed on positive PTs after local anesthesia with 2% lidocaine without epinephrine. Skin fragments were fixed on formalin for 24 h, processed for routine light microscopy and stained with hematoxylin and eosin. Additionally, paraffinated sections of skin biopsies from two cases were processed for immunohistochemistry using antibodies to T cell markers (CD3, CD8, CD56, and granzyme B).

Histology slides were randomly and independently analyzed by two experienced dermatopathologists (OT and JCC) with no knowledge of the clinical pattern of CADR or the morphology of the patch tests. Apart from the general histopathologic pattern, specific morphological epidermal and dermal details were evaluated and quantified, namely the characteristics of the horny layer, the intensity of spongiosis, exocytosis, vesicles, pustules, and vacuolar changes in the basal epidermal layer, keratinocyte necrosis and inflammatory cells in exocytosis, characteristics and intensity of the lymphocyte, eosinophil or neutrophil infiltrate (distribution mainly in the upper or mid dermis, perivascular, interstitial, dermal-epidermal junction, or periadnexal), dermal edema, vasodilation, intravascular cells, and extravasated erythrocytes. Dermatopathologists independently rated each of these parameters between 0 (absent) and 6 (very intense) and the sum of their individual scores was calculated to grade the intensity of the parameter studied (maximum score 12).

Histopathologic aspects were correlated with the clinical pattern of the CADR and the macroscopic characteristics of the patch test.

Results

Patients and drug eruptions studied

We studied positive drug PTs from 16 patients, seven males and nine females, aged 43 to 86 years (mean 58.4 ± 12.5 years) with different clinical patterns of non-immediate CADR caused by antibiotics (8), other antimicrobials (2), anticonvulsants (4), and diltiazem (2), with onset 1-28 days after drug intake (mean 8.8 ± 7.2 days) (Table 1).

Acute generalized exanthematous pustulosis, diagnosed according to the RegiSCAR criteria,[47] developed within 1-7 days (mean 4.2 ± 2.8 days). Patient 1, with long-standing plaque-type psoriasis, developed three accesses of generalized pustular rashes, with accentuation in large body folds, shortly after using fluoroquinolones for urinary tract infections. The other culprits in AGEP were clindamycin, acyclovir (one case each), and diltiazem (two cases). MPE with no significant systemic symptoms was induced by antibiotics (amoxicillin- three cases, cefotaxime, cefoxitin, and ciprofloxacin- one case each) with a latency period of 2-7 days (mean 4.0 ± 2.0 days). Four cases of exanthema, fever, hepatic cytolysis, eosinophilia, lymphadenopathy, and aggravation of renal function or digestive symptoms that fulfilled RegiSCAR criteria for DRESS[48] were induced by carbamazepine (2), phenytoin (1), and abacavir (1) and developed 10-28 days after initiating therapy (mean 20.5 ± 7.7 days). A case of TEN

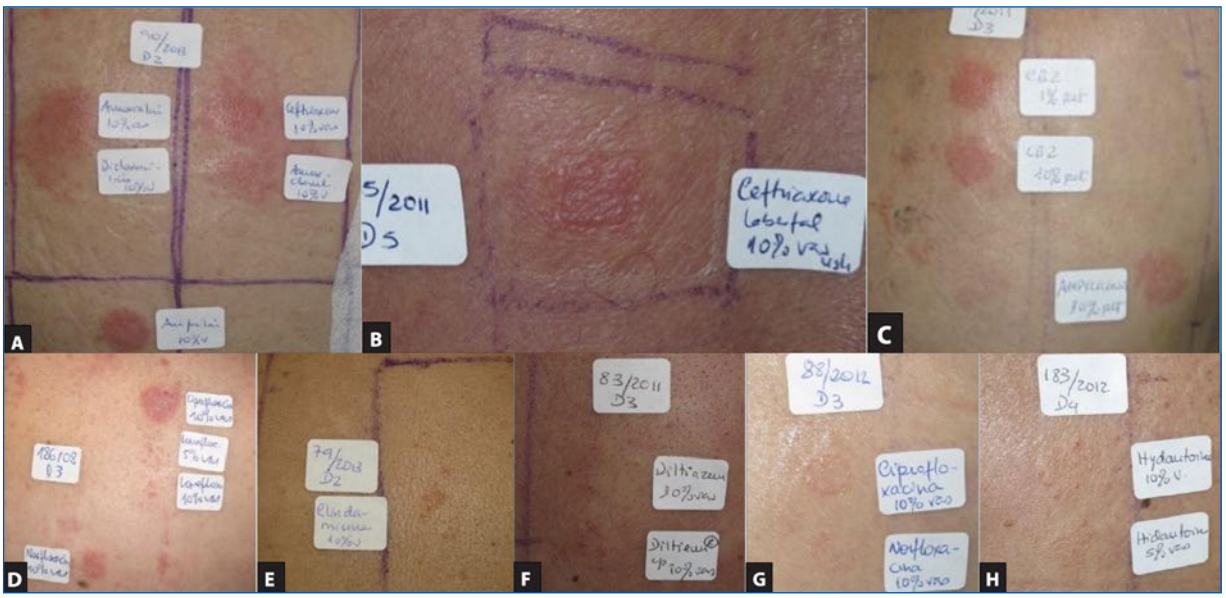

Figure 1. A and **B:** macroscopic aspects of positive patch tests with drugs with different clinical patterns. Erythema, papules and/or vesicles covering and exceeding the patch test application area in MPE from aminopenicillins and cephalosporins, **C:** DRESS from carbamazepine, **D:** pustules in a PT from ciprofloxacin and norfloxacin in AGEP from ciprofloxacin, **E:** minor pustules with no underlying erythema in two cases of AGEP from clindamycin, **F:** diltiazem, **G:** an "edge effect" with ciprofloxacin and norfloxacin in MPE from ciprofloxacin and **H:** a papulovesicular reaction with faint erythema to different concentrations of phenytoin.

with skin detachment involving > 50% of the total body surface area was caused by carbamazepine used for the treatment of seizures from meningioma (Table 1).

Macroscopic features of positive patch tests

Positive PT with the culprit drug and/or related substances was rated between 1+ and 3+ in 13 cases with erythema and infiltration covering the whole patch test area or extending beyond it (5), but with other morphologic aspects: papules and vesicles (10) in MPE or DRESS, pustules over erythema (4) or scattered isolated pustules (1) in AGEP, and confluent vesicles with a central area of skin detachment and Nikolsky's sign in the case of TEN from carbamazepine (Table 2; * Fig. 1).

Histopathology of positive patch tests

Skin biopsies collected from positive PT on D3 (14 cases) or D4 (2 cases) showed epidermal spongiosis and exocytosis, as well as a perivascular lymphocyte infiltrate in the upper dermis in all 16 cases, but with variable intensity and in particular combinations in the cases of AGEP (Fig. 2 and 3), MPE (Fig. 4), DRESS (Fig. 5 and 6) and TEN (Fig. 7) (Tables 3 and 4).

Epidermal Changes

The horny layer was parakeratotic in three cases (18.8%) and orthokeratotic in 13 (81.3%), with focal parakeratosis in two. Intracorneal and/or subcorneal pustules were observed in four cases of AGEP (Figures 2 E-H and 3 D and E) and in two cases of MPE, one associated with significant lymphocyte and neutrophil exocytosis forming vesicles. Acanthosis occurred in the psoriatic patient with AGEP (Fig. 2G) and in another AGEP patient with no previous dermatological disease.

Vesicles, absent in AGEP, were observed in all PTs from DRESS (Figures 5 B and 6 B) and TEN (Fig. 7 C) and in 3/6 MPE. They were more pronounced in DRESS and TEN than in MPE (Table 5) and in PTs from anticonvulsants (data not shown).

Spongiosis varied from very mild in a case of AGEP (0.5) to very intense (score 10 and 12) in 2 cases of DRESS (Figs. 5C and D) with a higher score in DRESS (7.3 ± 3.8) than in MPE (5.0 ± 2.1) or AGEP (3.5 ± 0.6) (Tables 3 and 5). The intensity of exocytosis was similar in all patterns but was due either to neutrophils (six cases–37.5%), as the only cell in 2 AGEP cases, or to lymphocytes (14 cases–87.5%), as the exclusive cell in 9 (56.3%) or in association with eosinophils in two. In three patients, lymphocyte exocytosis occurred in small

Table 1. Characteristics of the patients, the culprit drug, reason for its prescription, interval to the onset of the CADR and the pattern of the CADR that motivated patch testing

pt.	Age	Sex	Culprit drug	Reason for prescription	Interval (days)	Clinical pattern	Particular aspects
1	65	F	Ciprofloxacin	Recurring UTI	1	AGEP	Psoriasis; *2 previous pustular eruptions with fluorquinolones
2	53	M	Acyclovir	Herpetic retinitis	4	AGEP	
3	48	F	Clindamycin	Genital infection	7	AGEP	Also used amoxicillin
4	49	M	Diltiazem	Arterial hypertension	2	AGEP	
5	57	M	Diltiazem	Arrhythmia	7	AGEP	
6	64	M	Ceftriaxone	Surgery-single dose prophylaxis	3	MPE	Previous CADR after ceftrx. for polytrauma
7	86	F	Amoxicillin	not specified	7	MPE	Targets; *elevated liver enzymes
8	73	F	Ciprofloxacin	Genital surgery prophylaxis	2	MPE	
9	43	M	Cefazolin	Erysipela	6	MPE	Concomitant use of clindamycin for 5 days
10	53	F	Amoxicillin	Dental implant	3	MPE	Facial edema, vesicles
11	60	F	Amoxicillin	ENT complaints	3	MPE	
12	51	M	Carbamazepine	Epilepsy	20	DRESS (definite)*	MPE with atypical targets
13	48	M	Abacavir (HAART)	AIDS	10	DRESS (definite)*	HLA-B*57.01^{+}
14	69	F	Phenytoin	Sub-arachnoid haemorrhage	24	DRESS (probable)*	
15	70	F	Carbamazepine + Amoxicillin	Cerebral haemorrhage	28	DRESS (definite)*	HLA-A*31.01^{+} CADR to phenytoin amoxicillin at initial DRESS symptoms
16	46	F	Carbamazepine	Meningioma-post surgery	15	TEN	SCORTEN 2 at admission; * ± 50% BSA

UTI: urinary tract infections; *ENT: ear-nose-throat; *HAART: highly active anti-retroviral therapy; *MPE: maculopapular exanthema. **According to RegiSCAR criteria these DRESS cases could be defined as probable or definite, respectively with 5 or > 6 criteria[48]; *+HLA conferring a risk factor for severe CADR from abacavir and carbamazepine[22,49]; *SCORTEN: prognostic score for TEN[50].

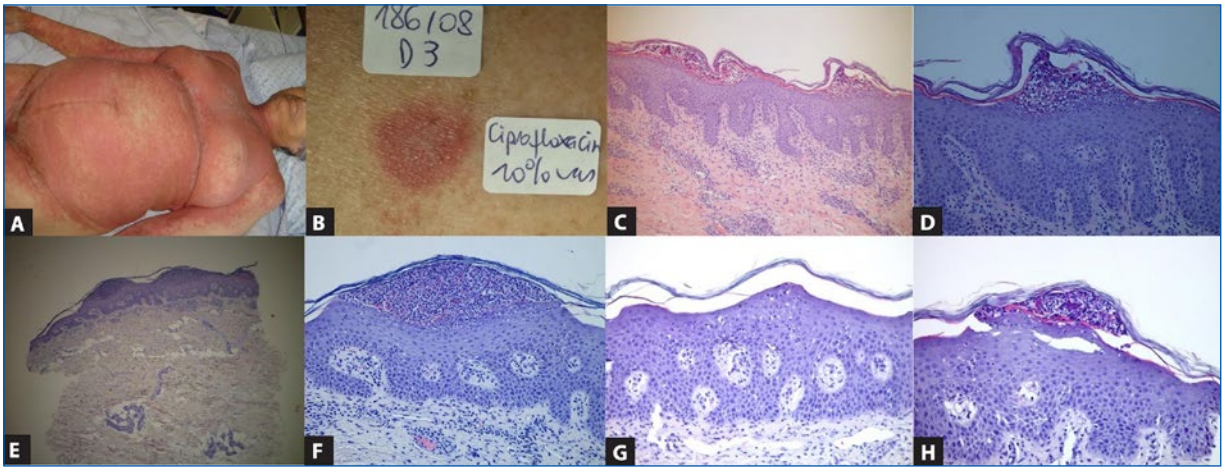

Figure 2. A: patient with psoriasis who developed AGEP from ciprofloxacin, **B:** with a pustular patch test. Remarkable similarity between intraepidermal/subcorneal spongiform pustules observed during the acute episode (**C, D:** H&E 40x, 100x) and in the patch test (**E, F:** H&E 25x, 100x). There was also acanthosis and intense neutrophil exocytosis towards a subcorneal pustule in the test (**G, H:** H&E 100x).

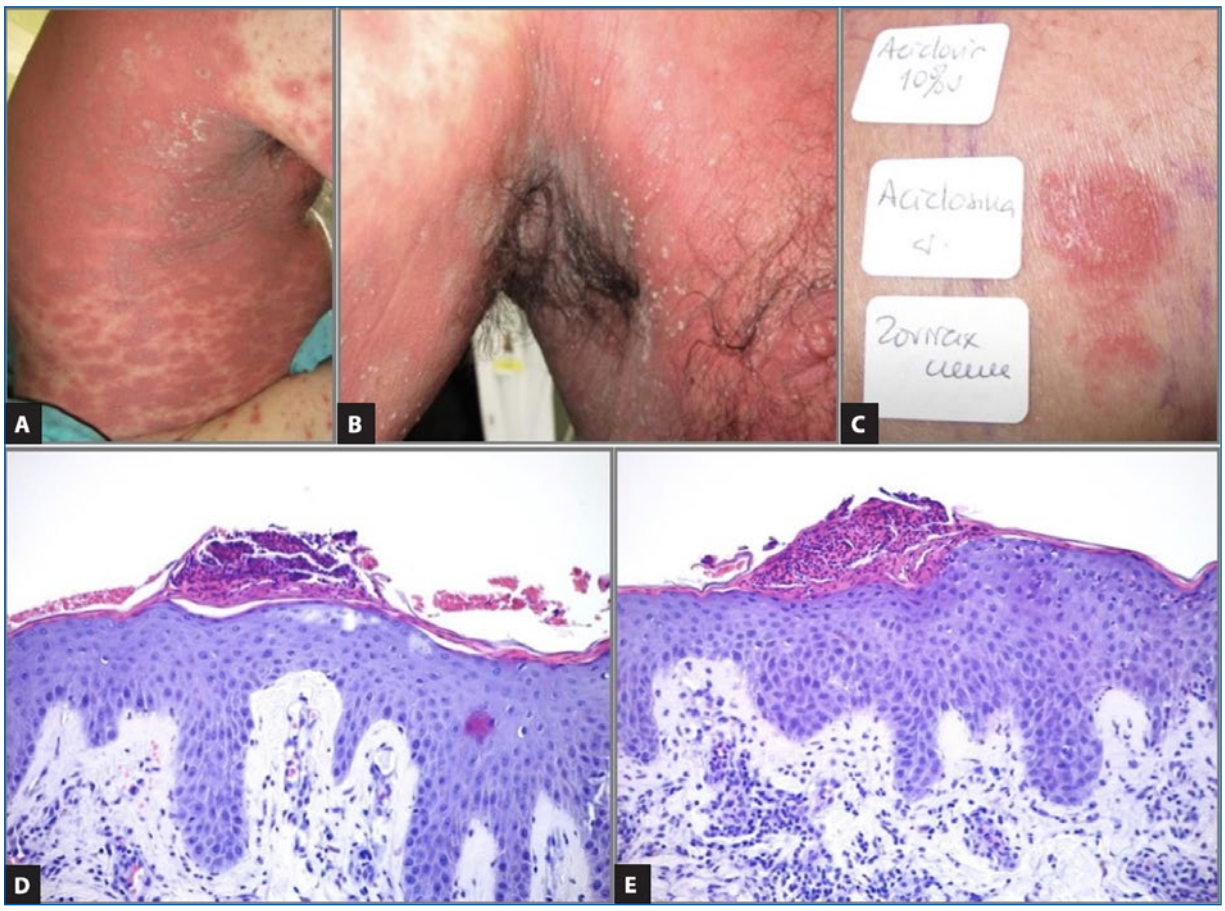

Figure 3. A and **B:** pustules mainly in large body in a case of AGEP **from acyclovir**, **C:** a pustular patch test to the commercial cream containing acyclovir. **D** and **E:** histopathology of the PTs (H&E 100x) showed intracorneal and subcorneal pustules with dermal edema, vasodilation, erythrocyte extravasation and intravascular lymphocytes eosinophils and neutrophils.

groups of cells, forming nests in two DRESS cases (Fig. 6E). Clusters of Langerhans/histiocytic cells were observed around vesicles in two cases (Fig. 4E and 5G).

Vacuolization of basal keratinocytes observed in 11 cases (68.8%) (Figures 4 F-J and 6 D and E) was more intense in TEN (score 12) than in DRESS (mean score 2.8 ± 2.9) or other CADR. Keratinocyte necrosis occurred in the 3+ positive PTs in DRESS from abacavir (Figs. 6D and F) and, particularly, in TEN from carbamazepine, where it involved the whole epidermal thickness with lymphocytes surrounding necrotic keratinocytes (Tables 3 and 5) (Fig. 7).

Dermal changes

Dermal edema occurred in 13 patients (81.3%) and was particularly significant in TEN. A perivascular lymphocytic infiltrate in the upper dermis was observed in all cases (Figures 4 I, 5 F, and 6 B and C) and extended to the reticular dermis in seven (43.8%) and deeper in one, occasionally with eosinophils (4) and neutrophils (3). Inflammation was interstitial in 13 cases (81.3%) and/or at the dermal-epidermal junction (14-77.7%) (Figure 4 B-J, 5 E, and 7 D), occasionally also around follicles (4-25.0%), eccrine glands (4-25.0%), both at the acrosyringia and the deeper lobules and around nerves (1). Inflammation scored as the average of the intensity in main dermal localizations, which was higher in TEN (23.0) followed by DRESS (13.0), MPE (12.8), and AGEP (7.0). In TEN, $CD8^+$ T cells predominated both in the dermis and epidermis, some expressed the cytotoxic marker CD56, but few stained for granzyme B (Figure 7 H-J). In DRESS from abacavir, $CD8^+$ cells were predominant and accumulated particularly below the areas with more epidermal aggression. (Figure 6H-J).

There were no signs of vasculitis, although extravascular erythrocytes were observed in seven cases

Table 2. Patch test results with culprit drugs, their morphology, and reactivity to related drugs

pt.	Culprit drug	Clinical pattern	Test material	Test score	Morphology	Positive PT with other drugs
1	CIP	AGEP	CIP 10% pet*	2+	Papules (D2);* flaccid pustules (D3)	Norfloxacin 10% pet* lomefloxacin 10% pet**
2	ACY	AGEP	Zovirax cream®	2+	Pustules "edge effect"	Other acyclovir commercial creams
3	CLI	AGEP	CLI 10% pet*	2+	Scattered papulo- pustules not covering the whole PT area	
4	DTZ	AGEP	DTZ 10 % pet*	2+	Infiltration with discrete pustules	
5	DTZ	AGEP	DTZ 10 % pet*	1+	Discrete erythema with pustule	
6	Ceftriaxone	MPE	cefotaxime 10%*	2+	Vesicles exceeding PT area	Ceftriaxone 10% pet***
7	AMX	MPE	AMX 10% pet*	2+	Papules and discrete vesicles	Ampicillin 10% pet*
8	CIP	MPE	CIP 10% pet*	1+	Papules "edge effect"	Norfloxacin 10% pet*
9	Cefazolin	MPE	cefoxitin 10% pet**	2+	Papules discrete vesicles	Cefazolin 10% pet*
10	AMX	MPE	AMX 10% pet*	2+	Vesicles exceeding PT area	Ampicillin 10% pet*
11	AMX	MPE	AMX 10% pet*	2+	Vesicles exceeding PT area	Ampicillin 10% pet* dicloxacillin 10% pet* ceftriaxone 10% pet*
12	CBZ	DRESS	CBZ1, 10% pet*	2+	Papules discrete vesicles	Ampicillin 10% pet* amoxicillin 10% pet*
13	Abacavir (HAART)	DRESS	Ziagen® 10%pet***	3+	Confluent vesicles widely exceeding PT area	
14	PHY	DRESS	PHY 10% pet*	1+	Faint erythema papules	PHY 5% pet**
15	CBZ + AMX	DRESS	CBZ1, 10%pet*	2+	Vesicles exceeding PT area	
16	CBZ	TEN	CBZ 1, 10%pet*	3+	Exuberant reaction confluent vesicles	CBZ 20%pet**

PT: patch test; *CIP: ciprofloxacin, ACY: acyclovir, CLI: clindamycin, DTZ: diltiazem, AMX: amoxicillin, CBZ: carbamazepine, PHY: phenytoin, ALP: allopurinol; *pet: petolatum; **allergens from Chemotechnique Diagnostics; ***pure chemicals prepared in house; ****freshly prepared powder of the pills.

(43.8%), and leukocytoclasia occurred in a MPE from cephalosporin. Intravascular erythrocytes or neutrophils were observed in all patients, in one case well aligned along a blood vessel.

Correlation of PT histopathology with the pattern of CADR

In 4/5 PTs from AGEP, we observed intraepidermal or subcorneal spongiform pustules with neutrophil exocytosis in two cases and lymphocyte exocytosis in all cases, a histopathologic pattern was very similar to the acute CADR, as shown in patient 1 (Fig. 2). Moderate spongiosis was observed in all cases, mostly without vesicles, necrotic keratinocytes or vacuolization of the basal layer. The dermal infiltrate was mostly perivascular, constituted mainly by lymphocytes and with associated neutrophils in 2/5 cases (Fig. 2 and 3).

In MPE, the most striking feature was the vacuolization of the basal epidermal layer, associated with spongiosis and lymphocyte exocytosis in all cases but forming intraepidermal vesicles only in three. No necrotic keratinocytes were observed. There was a predominantly perivascular dermal infiltrate of lymphocytes, some also present at the dermal-epidermal junction, with very occasional eosinophils or neutrophils (Fig. 4).

In the four cases of DRESS, there was an intense spongiosis with lymphocyte and/or mixed cell exocytosis, forming intraepidermal vesicles, very large in two (Figure 5 B-D) and lymphocyte exocytosis forming epidermal nests reminiscent of Pautier's microabscesses of mycosis fungoides (Fig. 6E) Lymphocyte infiltration was mainly perivascular and interstitial, less intense at the dermal-epidermal junction, and occasionally also peridanexal (2/4) and perineural (1/4). Epidermal exocytosis or interstitial infiltration of eosinophils occurred in two cases (Fig. 6 and 7).

The most significant characteristic of the TEN test was the full-thickness epidermal necrosis, with lymphocytes

Table 3. Epidermal changes in skin biopsies of positive patch tests

pt	Clinical pattern	Horny layer	Spongiosism	Exocytosis	Main cells	Vesicles	Pustules	Main localization	Necrosis	Vacuolation
1	AGEP	OtK	3	6	Neut	0	4*	Intra-subcorneal	0	0
2	AGEP	Pkt	3	6	Neut	0	10*	Intra-subcorneal	0	2
3	AGEP	OtK/Pkt	4	2	Ly	0	3	Follicullar infindibula	0	0
4	AGEP	Pkt	4	4	Ly Neut	0	6	Subcorneal	0	0
5	AGEP	OtK	0.5	3	Ly	0	0		0	0
6	MPE	OtK	8	4	Ly	4	0	Acro-syringium	0	4
7	MPE	OtK	4	7	Ly	1**	4	Eccrine channel	0	8
8	MPE	OtK	6	4	Ly	0	0		0	1+
9	MPE	OtK/Pkt	6	8	Ly Neut	5	4	Intra-subcorneal	0	1
10	MPE	OtK	4	6*	Ly	0	0		0	2+
11	MPE	OtK	2	2.5	Ly	0	0		0	0.5+
12	DRESS	OtK	4	8*	Ly Eos++	12	0		0	3
13	DRESS	OtK	12	9*	Ly Neut Eos	12	0		5	6
14	DRESS	OtK	3	3	Ly	2**	0		0	2+
15	DRESS	OtK	10	6	Ly	12	0		0	0
16	TEN	Pkt	3	8	Ly Neut	8	0		12	10
%		O-81% P-31%	100%	100%	L-87.5% N-37.5% E-12.5%	50%	37.5%		12.5%	68.8%

*pet: petolatum; **allergens from Chemotechnique Diagnostics; ***pure chemicals prepared in house; ****freshly prepared powder of the pills.
AGEP - Acute generalized exanthematous pustulosis, MPE - maculopapular exanthema; DRESS - Drug reaction with eosinophilia and Systemic Symptoms; OtK - orthokeratosis; PkT - parakeratosis; Ly - lymphocytes; Neut - Neutrophils; Eos - eosinophils;

surrounding necrotic keratinocytes as in "satellite cell necrosis." Marked subepidermal edema and large unilocular subcorneal vesicles with necrotic keratinocytes around them were also observed in a limited area of the skin biopsy (Fig. 7).

Discussion

PT is usually performed in delayed CADR to identify the culprit drug, but a skin biopsy is seldom performed. Therefore, apart from occasional case reports, most from AGEP, there are very few descriptions of the histopathology of patch tests in CADR. In this study, we included 16 patients with positive drug PT in different clinical patterns of CADR and PT showed features that simulated the acute eruption, both macroscopically and on histopathology. Apart from erythema, infiltration and vesicles typical of ACD, drug PTs showed different morphologic patterns, namely vesicle confluence and skin necrosis with Nikolsky's sign in TEN and pustules in AGEP.

The main histopathologic changes observed in drug PTs spongiosis, lymphocyte exocytosis forming vesicles, a dermal inflammatory infiltrate with perivascular and interstitial lymphocytes, occasional eosinophils and extravasation of erythrocytes, is also the pattern usually described in PTs with contact allergens[49]. Nevertheless, apart from these common findings, drug PT has particular histopathologic aspects that are not typical of ACD, namely subcorneal pustules, basal cell vacuolization and necrotic keratinocytes, which are more characteristic of T cell-mediated drug eruptions[50].

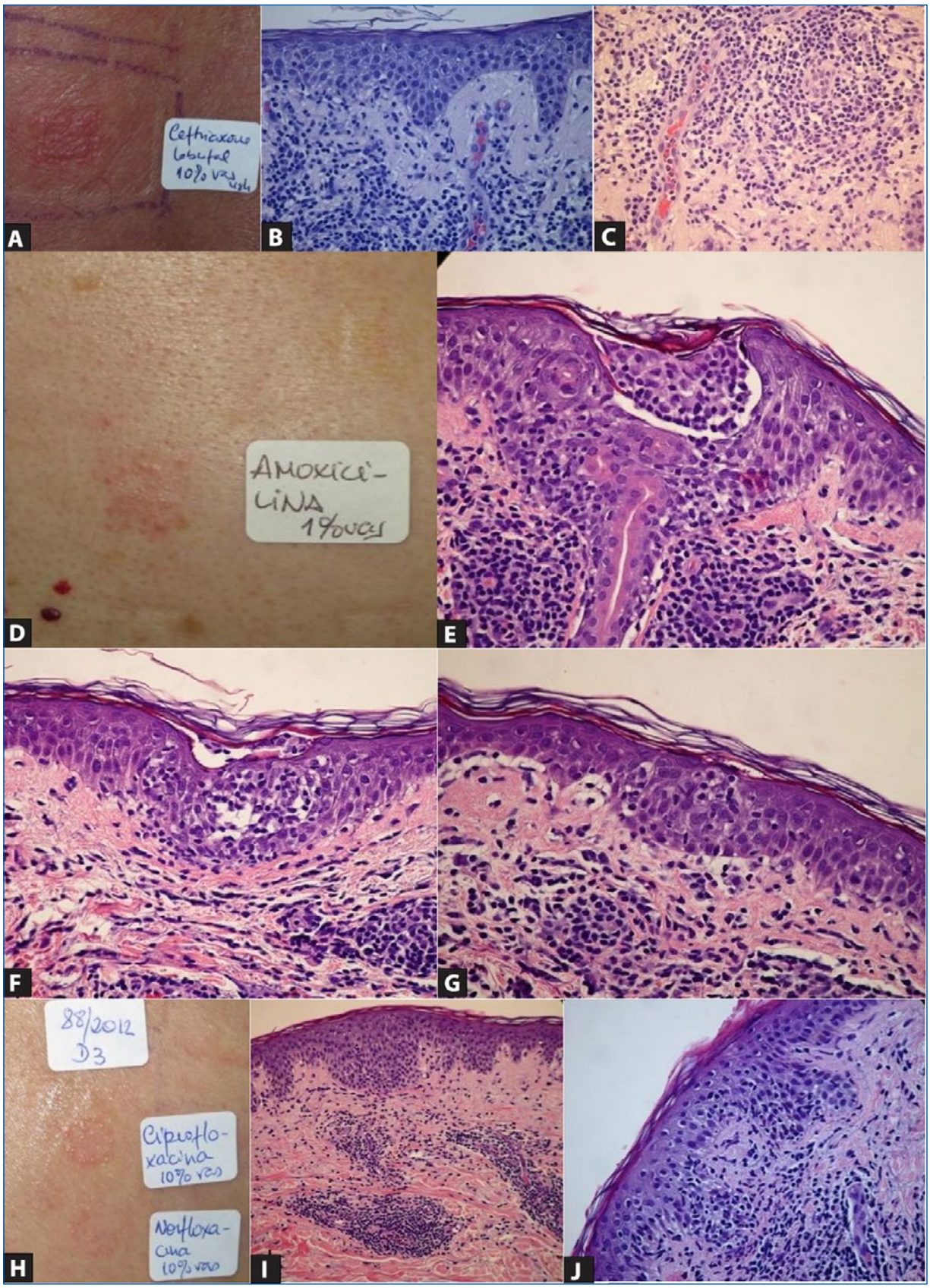

Figure 4. A: positive patch tests in cases of MPE from ceftriaxone, **B:** amoxicillin, **H:** ciprofloxacin that on histopathology (H&E 40-200x) showed significant vacuolization of basal cells (**B**, **G**, **J**), **F:** lymphocyte exocytosis forming small vesicles or **E** and **G:** clusters of histiocytes, **B** and **C:** a dense dermal infiltrate with intravascular neutrophils.

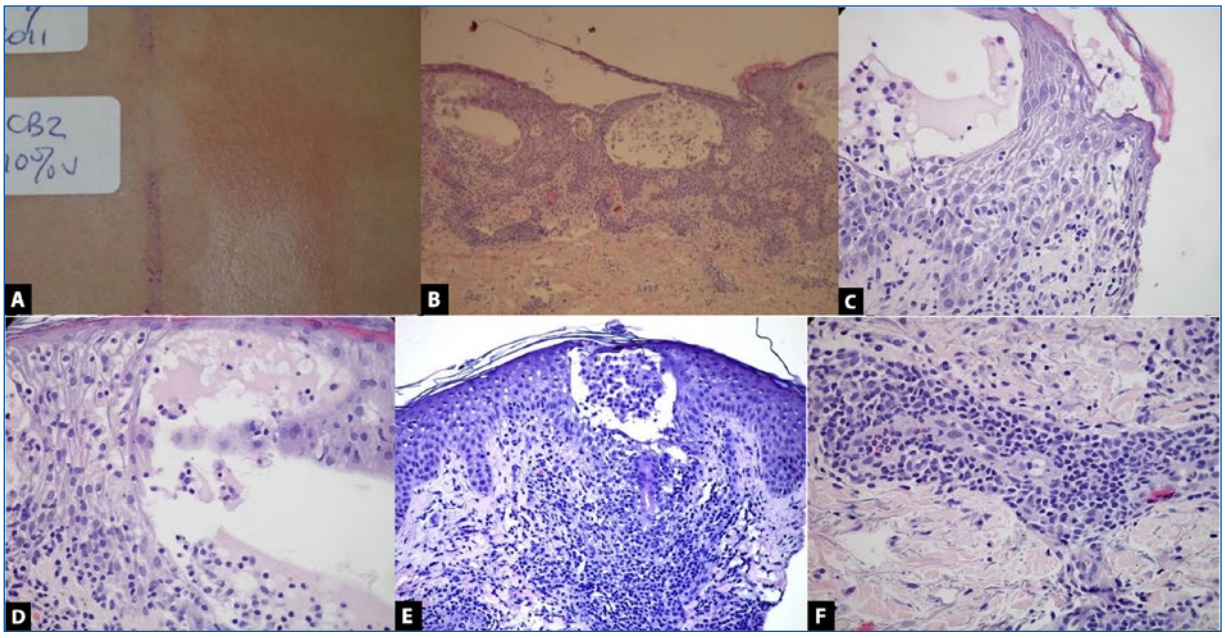

Figure 5. A: positive patch test from carbamazepine in a case of DRESS with remarkable spongiosis and many vesicles (**B**-**D:** H&E 40x-200x), clusters of histiocytes within the vesicles (**E:** H&E 100x) and a dense dermal inflammatory infiltrate with eosinophils (**F:** H&E-200x).

Moreover, histopathology of positive drug patch tests shared many features with acute CADR. PTs in AGEP showed neutrophilic exocytosis and intraepidermal pustules with a spongiform pattern, as previously reported[34,51-54]. Nevertheless, lymphocytes were the main cell in exocytosis and in the dermal inflammatory infiltrate, which is in agreement with the understanding that drug-specific T cells, particularly Th17, are the main effector cells in AGEP. They infiltrate the skin during the CADR, and interleukin (IL-17) activates keratinocyte secretion of IL-8/CXCL8 that, directly or indirectly through IL-17 and IL-22, attract neutrophil to the epidermis and, along with granulocyte-macrophage colony-stimulating factor, enhances epidermal survival of neutrophils and pustule formation[47,55-57]. This also occurs in pustular PTs from contact allergens, like nickel, related to the secretion of high amounts of IL-17 by some Ni-specific T cells[58,59] and may explain the intraepidermal pustules in the positive PTs in AGEP.

In PTs from MPE, we observed mainly a perivascular and dermal interstitial lymphocyte infiltrate, spongiosis, and exocytosis, and very particularly, vacuolization of the keratinocytes in the basal layer very similar to the histopathologic changes described early during the course of MPE in two studies involving 48 and 35 patients[50,60]. Dermal edema, extravascular erythrocytes and neutrophils in the lumina of blood vessels, observed by us respectively in 67, 67, and 100% of the PT, were also present in Naim's study, respectively in 85%, 28% and 38% of their 60 biopsies of MPE[50]. On the contrary, we found no necrotic keratinocytes in PT from MPE, reported in 22% of Naim et al. cases[50], but this may be explained by his inclusion of cases of exanthema associated with DRESS, where we found such a pattern.

Actually, histopathologic findings in positive PTs in DRESS were similar to MPE, although more intense and with scattered necrotic keratinocytes, reflecting a higher aggressive capacity of T cells that cause a more severe and long-lasting exanthema[61]. Necrotic keratinocytes are also observed in skin lesions during the acute exanthema of DRESS, and according to Walsh et al., they are associated with the worst prognosis and more severe hepatic cytolysis[62], although we could not confirm it[63]. Necrotic keratinocytes were particularly important in a PT from abacavir, with predominantly $CD8^+$ T cells, some migrating to the epidermis where they colocalized with necrotic keratinocytes, suggesting a direct cytotoxic mechanism. This is in agreement with the participation of $CD8^+$ cytotoxic T cells in abacavir hypersensitivity, as these cells recognize the drug in association with HLA-B*57:01[64,65], the HLA haplotype also present in our patient. Both in PTs and in the acute exanthema in DRESS, lymphocyte infiltration formed a dense perivascular and/or interstitial infiltrate, with significant exocytosis forming epidermal microabscesses, as in cutaneous T cell lymphoma/mycosis fungoides, but with no atypical

Table 4. Dermal changes in skin biopsies of positive patch tests

pt	Clinical pattern	Histology nº	Localization	Edema	Dermal infiltration						Extrav RBC
					Peri-vasc	Inters-titial	DEJ	Periadnexal		Main cells	
1	AGEP	64572	DS	4	3	3	2	0		Neut Ly	0
2	AGEP	71602	DS	4	6	5	0	0		Ly	0
3	AGEP	76790	DS/DR	0	2	0	0	7	folic	Ly	0
4	AGEP	69376	DS	3	6	4	0	0		Ly Neut	0
5	AGEP	71785	DS	2	4	0	0	0		Ly	0
6	MPE	72406	DS	6	9	5	3	2	acr-syr	Ly Eos	0
7	MPE	72805	DS++/DR	0	8	4	2	5	acr-syr	Ly	2
8	MPE	74128	DS	3	7	3	2	0		Ly	1
9	MPE	74178	DS++/DR	2	6	4	3	2	folic	Ly Neut	6
10	MPE	76089	DS	0	6	0	3	0		Ly	0
11	MPE	76881	DS++/DR	2	5	6	1	8	folic	Ly Eos	1
12	DRESS	73380	DS++/DR	1	7	2	3	0		Ly	10
13	DRESS	71825	DS/DR/DD	6	10	8	2	3	folic	Ly Eos*	0
14	DRESS	74806	DS/DR	4	6	1	1	4	acr-syr	Ly	0
15	DRESS	74027	DS	4	5	4	3	0		Ly	6
16	TEN	66661	DS	10	8	9	6	2	peri-eccrine	Ly Eos*	8
%				13/16 81.3%	16/16 100%	13/16 81.3%	12/16 75.0%	8/16 50%		L-100% N-18.8% E-25.0%	7/16 43.8%

DS/DR/DD: dermis superficialis, dermis reticularis, deep dermis:
DEJ: dermal-epidermal junction;
*RBC: red blood cells;
*Ly: lymphocytes, Neut: neutrophils, Eos: eosinophils;
*folic: follicular; acr-syr: acrosyringeal,
*eosinophils mainly in the interstitial dermis.

cells or a pseudolymphomatous reaction, as occasionally observed in the acute exanthema[63,66]. Eosinophilia, a hallmark of DRESS, is not associated with a prominent skin infiltration by eosinophils, neither during the acute eruption[63] nor in the PTs we studied.

Globally, histopathology findings from DRESS and MPE are quite similar both during the acute exanthema and in positive PT, particularly when considering basal cell vacuolization, exocytosis and the perivascular and dermal-epidermal infiltrate[50,46]. These similarities at the histopathology level may reinforce the idea of a possible continuous spectrum between DRESS and maculopapular exanthema, which is also suggested from the clinical presentation of these two CADR[67].

The single case of a positive patch test in TEN is a very good example of the histological similarity between the acute CADR and the skin test, which showed full-thickness epidermal necrolysis, the hallmark of TEN[68,69], and lymphocyte exocytosis with CD8+ T-cells surrounding necrotic keratinocytes, resembling satellite cell necrosis (satellitosis) as described in acute graft-versus-host disease and TEN[70,71]. This may represent direct cytotoxicity of drug-specific T cells that recognize and kill keratinocytes expressing HLA combined with the drug[72], although keratinocyte necrolysis in TEN is mainly mediated by soluble factors that may exert their necrolytic/apoptotic effect at a distance, like granulysin, FasL, TNF-α, and other TNF related death molecules[73-75].

Table 5. Mean scores for epidermal (a) and dermal (b) changes and their frequency (%) in patch tests from the different clinical patterns of CADR

a)

Clinical pattern	Epidermal changes											
	Spongiosis		Exocytosis		Vesicles		Pustules		Keratinocyte necrosis		Keratinocyte vacuolization	
AGEP	3.5 ± 0.6	100%	4.2 ± 1.8	100%	0	0%	4.6 ± 3.7	80%	0	0%	0.4 ± 0.9	20%
MPE	5 ± 2.1	100%	5.3 ± 2.1	100%	1.7 ± 2.3	67%	1.3 ± 2.1	33%	0	0%	2.8 ± 2.9	100%
DRESS	7.3 ± 3.8	100%	6.5 ± 2.3	100%	9.5 ± 4.3	100%	0	0%	1.3 ± 2.5	25%	2.8 ± 2.2	80%
SJS/TEN	3		8		8		0		12		10	

b)

Clinical pattern	Dermal changes									
	Edema		Extravascular RBC		Inflammatory infiltrate					
					Perivascular		Interstitial		DEJ	
AGEP	2.6 ± 1.7	80%	0	0%	4.2 ± 1.8	100%	2.4 ± 2.3	60%	0.4 ± 0.9	20%
MPE	2.2 ± 2.2	67%	1.7 ± 2.2	67%	6.8 ± 1.5	100%	3.7 ± 2.1	83%	2.3 ± 0.8	67%
DRESS	3.8 ± 1.7	100%	4.0 ± 4.1	50%	7.0 ± 1.8	100%	3.8 ± 3.0	100%	2.3 ± 0.8	100%
SJS/TEN	10		8		8		9		6	

RBC: red blood cells; DEJ: dermo-epidermal junction.

The combination of histopathologic findings, their relative proportion and intensity in PTs from different CADR suggests the contribution of different effector mechanisms in PTs as observed during the acute CADR where distinct T cell-phenotypes orchestrate the immuno-inflammatory effector skin reaction inducing different clinical patterns of CADR[76-79]. As drug-specific T cells isolated from positive patch tests were shown to have functional characteristics similar to those isolated from the skin during the acute eruption[43,80], it may be expected that patch tests also reflect, macro and microscopically, the variability in effector function of the different sub-phenotypes of drug-specific T cells that recognize the drug when it is applied in the skin during PT. This can support our findings with histopathologic changes in PT mimicking those usually observed in the corresponding type of CADR.

Conclusion

PT is a useful tool to confirm the culprit drug involved in non-immediate CADR and study cross-reactions, which is relevant for patient orientation. Also, as we have shown, PTs have macroscopic and histopathological findings that somehow simulate acute CADR. Therefore, they can be considered a form of a localized drug provocation test, which is safer than systemic provocation, although less sensitive[1].

The reduced number of PT reactions studied, and a very limited number in each clinical pattern of CADR is an important limitation of this study, but we could show that a positive patch test in a non-immediate CADR partially reproduces the clinical and histopathologic pattern of the corresponding CADR. This data, reinforced by the isolation of drug-specific T cells from positive patch tests with a phenotype similar to those found in the blood or on the skin during the acute eruption[43], support the possibility of using patch testing to study the main effector cells, their phenotype and aggressive machinery and evaluate how the cells use of their effector functions to produce the skin inflammation in non-immediate CADR.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in

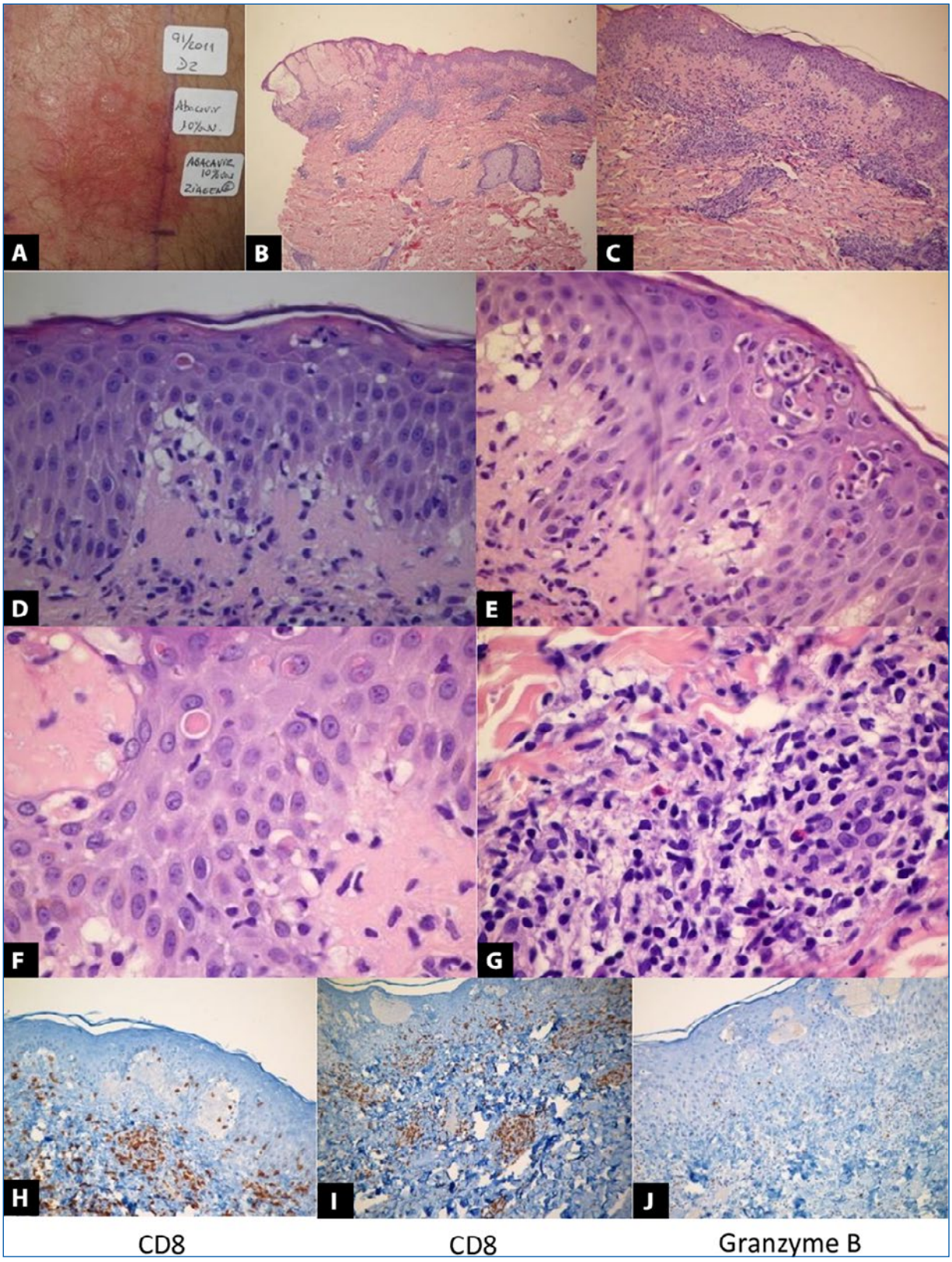

Figure 6. A: positive patch tests in DRESS from abacavir (Ziagen®) that on histopathology (H&E 25x-400x) showed, **B:** large vesicles and **C:** a dense perivascular lymphocyte infiltrate in the upper and mid-dermis, **D:** significant basal cell vacuolization, **F:** isolated necrotic keratinocytes, **E:** exocytosis of lymphocytes forming microabscesses and **G:** eosinophils within the dermal infiltrate, although there was no eosinophilia during the acute phase. $CD8^+$ T cells were predominant in the infiltrate, mainly below areas of more intense epidermal involvement, **I:** several $CD8^+$ T cells adjacent to necrotic keratinocytes. **J:** staining for granzyme B was relatively poor.

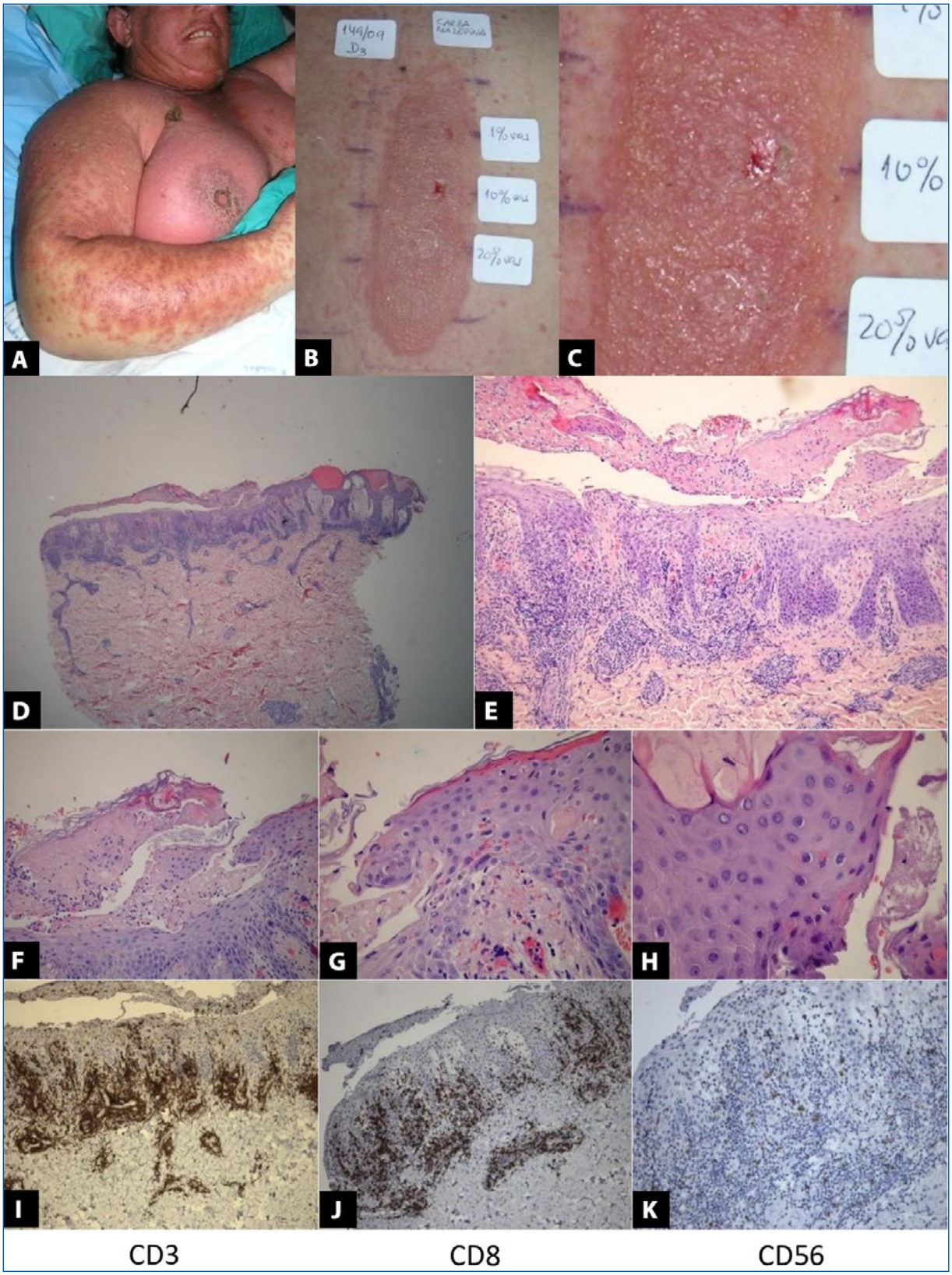

Figure 7. A: severe TEN from carbamazepine, **B:** positive patch testing with confluent vesicles and epidermal necrosis. **C:** histopathology of the patch test (H&E 25x-400x) showed many intraepidermal vesicles; **D:** necrosis involving the whole epidermal thickness; **E, F** and **G:** isolated or confluent necrotic keratinocytes often with adjacent lymphocytes. **H:** the infiltrate was mostly formed by CD3+ T cells, **I:** mainly $CD8^{+}$, both in the dermis and epidermis, **J:** reduced infiltration of $CD56^{+}$ cells.

accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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.

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Port J Dermatol and Venereol. **REVIEW ARTICLE**

Pathophysiology of hidradenitis suppurativa: a systematic review of the literature

Fisiopatologia da hidradenite supurativa: uma revisão sistemática da literatura

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Abstract

Hidradenitis suppurative (HS) is a multifactorial, recurrent, chronic inflammatory disease with a significant impact on patient's quality of life. The etiopathogenesis of this complex condition is not fully understood. In this systematic review, we aimed to address and clarify the role of genetics, immunity, endocrinology, and skin microbiome together with risk factors in HS etiopathogenesis. A systematic review, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was performed using PubMed® and Web of Science™ databases on December 3rd, 2021, using patient/population, intervention, comparison and outcomes (PICO) criteria, limited to the last 10 years and English. Reports were analyzed by two independent reviewers. A total of 123 reports were included and divided into five sections: genetics, immunity, endocrinology, microbiome, and risk factors. Regarding genetics, up to 30-40% of patients have a positive family history of HS but only a small subset of these harbor genetic variants in components of the gamma-secretase complex. In fact, in more than 90% of HS patients, the genetic features contributing to disease development remain largely unknown. The immune response is also crucial for HS; it is characterized by antimicrobial peptide and proinflammatory cytokine dysregulation, namely interleukin (IL)—IL-23, IL-12, and Th17 immune response. This immune response in local and, consequently, systemic inflammation is amplified in patients with metabolic syndrome. The relationship between metabolic syndrome and HS is clear, and patients with metabolic syndrome have a higher risk of developing HS. The most recent evidence also associates skin microbiota dysbiosis with HS pathogenesis, contributing to local and systemic inflammation. Besides these intrinsic factors, the role of lifestyle in the development of HS is well accepted. Tobacco smoking and obesity are the main risk factors identified as contributing to HS pathogenesis. Chronic inflammation characterizes HS, a debilitating condition with a complex and multifactorial etiopathogenesis. The current model integrates genetics, immunity, endocrinology, and skin microbiome. Notwithstanding, efforts should be made to improve our comprehension of HS etiopathogenesis, hopefully leading to the development of more effective treatments.

Keywords: Gamma-secretase complex. Etiopathogenesis. Risk factors. Hidradenitis suppurativa. Immunity. Microbiome.

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Resumo

A hidradenite supurativa (HS) é uma doença inflamatória, multifatorial, recorrente e crónica com um impacto significativo na qualidade de vida dos doentes. A etiologia desta condição complexa não é totalmente compreendida. Nesta revisão sistemática, pretende-se abordar e clarificar o papel da genética, imunidade, endocrinologia, microbioma cutâneo e fatores de risco que contribuem para o desenvolvimento da HS. A revisão sistemática, seguindo as orientações PRISMA, foi realizada através de uma pesquisa bibliográfica nas bases de dados PubMed® e da Web of Science™ a 3 de dezembro de 2021, utilizando critérios do PICO, e limitada aos últimos 10 anos e inglês. Os estudos a serem incluídos foram analisados por dois revisores independentes. Um total de 123 estudos foram selecionados e divididos em cinco secções: genética, imunidade, endocrinologia, microbioma e fatores de risco. Em relação à genética, cerca de 30-40% dos doentes têm uma história familiar positiva de HS, mas as variantes genéticas das componentes do complexo da gama secretase só estão identificadas num número reduzido de doentes. De facto, em mais de 90% dos doentes com HS, a componente genética que contribui para o desenvolvimento da doença permanece desconhecida. A resposta imunitária é também crucial para a HS: caracteriza-se pela desregulação dos péptidos anti-microbianos assim como das citocinas pró-inflamatórias, nomeadamente IL-23, IL-12 e resposta Th17. Esta resposta que ocorre na inflamação local e consequentemente sistémica é exacerbada em doentes com síndrome metabólica. A relação entre a síndrome metabólica e a HS é clara, e os doentes com síndrome metabólica tem um risco elevado para o desenvolvimento de HS. As evidências mais recentes correlacionam também a disbiose do microbioma cutâneo com a patogénese da HS, contribuindo para a inflamação local e sistémica. Além destes fatores intrínsecos, o papel do estilo de vida no desenvolvimento da HS está bem estabelecido. O tabagismo e a obesidade são os principais fatores de risco identificados que contribuem para a patogénese da HS. A inflamação crónica caracteriza a HS, uma condição debilitante com uma etiologia complexa e multifatorial. O presente modelo integra a genética, a imunidade, a endocrinologia e o microbioma cutâneo, e poderá contribuir para o desenvolvimento de tratamentos mais eficazes.

Palavras-chave: Complexo gamma-secretase. Etiologia. Fatores de risco. Hidradenite supurativa. Imunidade. Microbioma.

Introduction

Hidradenitis suppurativa is a multifactorial, recurrent, chronic inflammatory condition with a significant impact on a patient's quality of life. The epidemiology of HS is not well established, but some studies indicate a prevalence of 1% in the European population[1]. There is no available epidemiological HS data regarding the Portuguese population. A study by Santos et al. evaluated Portuguese hospitalized patients with HS and concluded that the highest incidence rate occurred between 20 and 29 years old in females and 40 and 49 years old in males[2].

The onset of the disease usually occurs after puberty. HS frequently affects apocrine gland-bearing skin, mainly in the axilla, groin, breast area, gluteal and perineal regions. The initial pathophysiology of HS is probably related to alterations of the infundibular epithelium leading to follicular "plugging" and subsequent stasis of follicular content, propagation of resident bacteria, and dilation of the hair follicle unit. This cascade occurs in a background of immune dysfunction, both innate and adaptive[3-6].

HS is frequently neglected, with a subsequent delay in diagnosis, which contributes to a dramatic decrease in patients' quality of life. The patient's delayed referral may have an impact on the optimal time frame for the beginning of treatment in a disease in which the sooner the treatment is started, the better the outcome will be.

The number of publications concerning HS has increased significantly in recent years as a direct consequence of increased awareness of the disease among clinicians of different specialties. Moreover, the knowledge regarding the contribution of genetics, microbiome, immunity, endocrinology, and environmental risk factors for the pathophysiology of the disease has advanced enormously (Fig. 1). Notwithstanding, it remains a complex condition with multifactorial etiopathogenesis that is yet to be fully understood, requiring a multidisciplinary approach[5].

The aim of this systematic review of the literature is to summarize the most recent advances in the knowledge of the pathophysiology of HS, thus contributing to a better understanding of the disease and, consequently, to improved management of patients with HS.

Methods

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)[7].

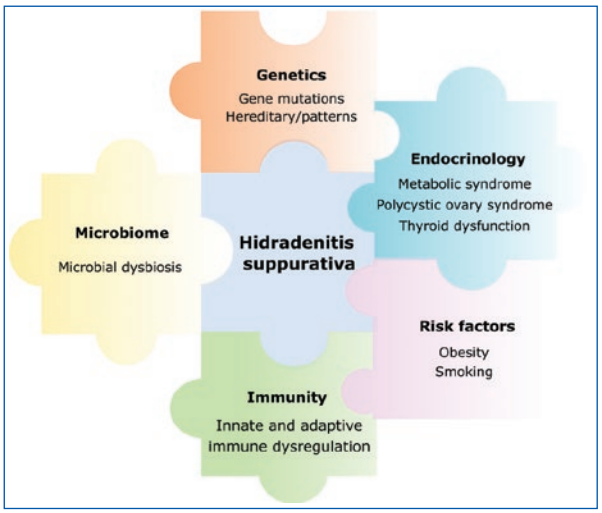

Figure 1. Overview of HS pathophysiology.

The PubMed® and the Web of Science™ databases were searched on December 3rd, 2021, using the strings "hidradenitis suppurativa AND (hormone* OR female hormone* OR androgen converting enzyme* OR obesity OR endocrinology OR contraceptive* OR androgen* OR estrogen* OR puberty OR hirsutism OR polycystic ovary syndrome OR finasteride)," "hidradenitis suppurativa AND (genetic* OR genetic signature OR gamma secretase (GSC) complex mutation* OR PSENEN OR PSEN1 OR NCSTN OR NOTCH)," "hidradenitis suppurativa AND (innate Immunity OR adaptative immunity OR cytokine* OR tumor necrosis factor alpha (TNF-α) OR IL-13 OR IL-23 OR IL-1 OR IL-17 OR IL-36 OR IL-6 OR autoimmunity OR follicular occlusion OR folicular rupture OR defensin* OR complement OR autoinflammation OR AMP*)," "hidradenitis suppurativa AND (skin microbiome OR microbiome OR pathogen* OR bacterial colonization OR biofilm* OR antibiotic*), hidradenitis suppurativa AND (risk factor* OR smoking OR nicotine OR electronic cigar* OR obesity OR intestinal inflammatory disease* OR rheumatologic* disease* OR professional risk OR labor risk OR occlusion OR friction OR hyperhidrosis OR cannabinoid*)," limited to papers written in English and published in the last 10 years. The papers obtained from these searches were joined and the duplicates were removed. Afterward, these papers were divided into five main fields that included endocrinology, genetics, immunity, microbiome, and risk factors. All the abstracts from each field were reviewed by two different authors. Reviews, case reports, and case series were not considered.

Results

A detailed flow chart with the results of the literature search is shown in Figure 2. We exported 4342 references from PubMed and Web of Science, and after the removal of duplicates and records without available abstracts, a total of 1277 references were retained. From this total of 1277 studies, divided into five main fields, 1168 were excluded by applying the selection criteria (959 by title and abstract and 209 that include treatment approach, which is out of the scope of the review). Fourteen additional studies were identified through reference tracking, citation, and grey literature. Finally, 123 studies were included in this review.

Genetics

Among patients with HS, up to 40% have a familiar history of the disease showing autosomal dominant inheritance with incomplete penetrance[8]. Causative monogenic mutations are rare and only explain 5% of HS cases[9]. Moreover, the family history of HS impacts the onset of the disease: early onset is associated with a family history of HS and with the development of inflammatory lesions at a higher number of body sites[10,11]. However, the full contribution of genetics has not been fully elucidated. A cross-sectional Dutch Twin Cohort showed that 1.2% (58 of 4686) of the twin pairs included in the study had HS with narrow-sense heritability of 77%[12]. The remaining variance is due to environmental factors supporting the multifactorial characteristic of the disease[12]. This polygenic and multifactorial pattern was recently corroborated in a nationwide registry study of Danish twins that estimated the relative importance of genetic and environmental factors underlying susceptibility to HS. This study showed that among the 170 twins with a HS diagnosis, gene-gene interactions are the likely cause of HS rather than unique mutations[9].

Some specific genes have been associated with the development of HS. GSC complex is a multi-subunit protease complex consisting of presenilin-1 (PSEN1)/presenilin-2 (PSEN2), presenilin enhancer gamma-secretase subunit (PSENEN), nicastrin (NCSTN), and anterior pharynx defective 1a (APH1A)/anterior pharynx defective 1b (APH1B). This complex is essential for the maturation of hair follicle cells and for normal immune system function[13]. Studies have demonstrated that loss-of-function mutations in the components of this complex lead to decreased protease cleaving activity, probably compromising canonical Notch signaling[14].

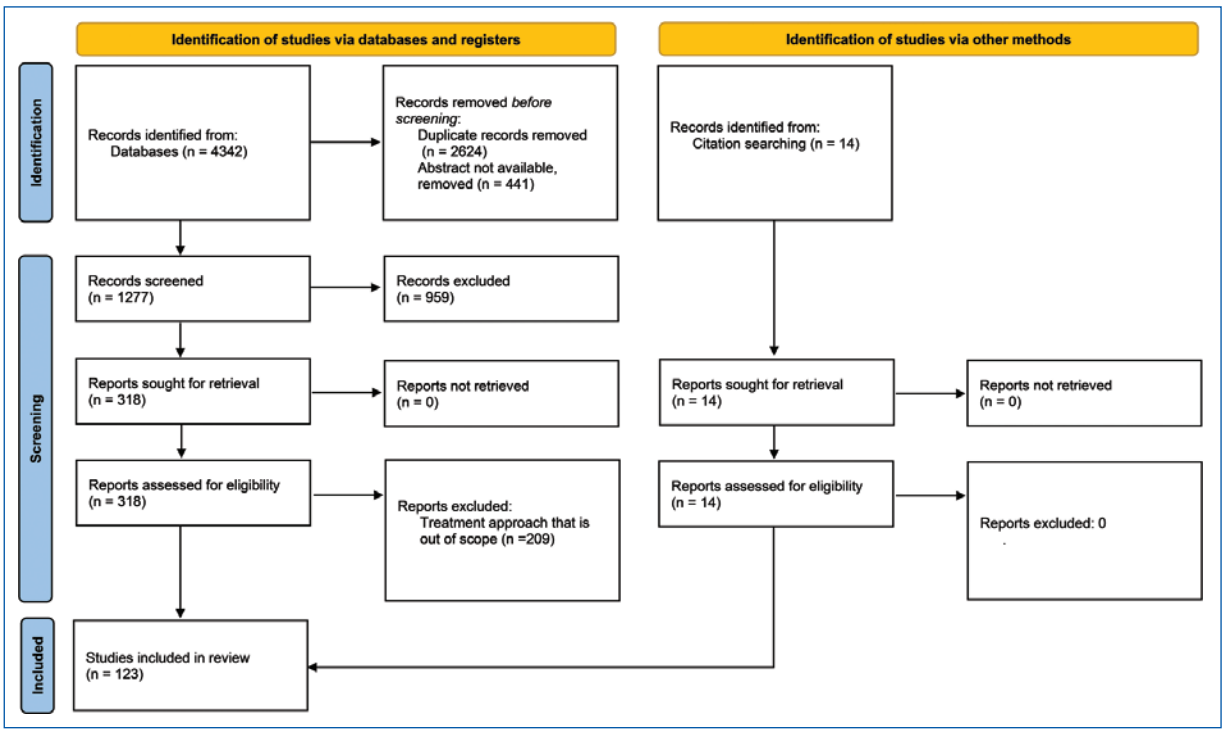

Figure 2. PRIMA flow for systematic review of the literature adapted from Page MJ (2021)[7].

The mutations in NCSTN are responsible for cases of familial HS by regulation of in vitro keratinocytes' inflammatory responsiveness through the Notch and PI3K/AKT signaling[8,15]. PSENEN mutations alone seemed to be insufficient to cause HS[3]. An in silico study demonstrated that mutations in GSC associated with HS have a structural impact and potentially also functional impact on the GSC, namely substrates receptor tyrosine-protein kinase (ErbB4), sodium channel subunit beta-1 (SCNB1), and tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (Tie1), that could contribute to a genetic signature of HS[16]. Besides the known loss-of-function mutation in the GS complex, a splice site mutation, c.582-1delG in NCSTN, was identified in Japanese familial HS[17].

Beyond these in vitro and in silico studies, there are also clinical studies aiming to address the genetic/genomic alterations in patients/families with HS. Apart from GSC genes, other genetic factors are also important in the pathophysiology of HS. Genes directly related to the IL-12/IL-23-Th17 pathway[18], β-defensin genes (namely DEFB4 and DEFB103)[19], sphingolipid metabolism pathway[20], DNA hydroxymethylation regulators[21], and human leukocyte antigen system (HLA)[22], have already been associated with HS (Table 1).

Immunity

HS should be classified as an immune-mediated disease.[5] The initial events in the development of HS can trigger an exaggerated response of the cutaneous immune system, resulting in the transformation of mild acute events into chronic inflammation of affected skin areas with the formation of recurrent nodules and dermal tunnels (Figure 3A)[5].

Disease progression can lead to systemic inflammation, amplifying the local inflammatory cascade and probably facilitating extracutaneous comorbidities.[5] Despite the consensus that immune dysregulation plays a major role in the development of chronic inflammatory lesions in HS, critical details such as specific cytokines and pathways involved, immune signature, and relative contributions from both innate and adaptative immune systems remain to be properly clarified. Figure 3B schematizes the findings in lesional and perilesional HS skin and relevant serum biomarkers reflecting the impact of immunity in the physiopathology of HS.

Innate immunity is crucial for developing HS[28,29]. This was demonstrated by the up-regulation of messenger RNA (mRNA) levels of antimicrobial peptides (AMP)[30] and proteins such as human-β-defensin 1 (hBD-1), hBD-2, and hBD-3, cathelicidin (LL-37), ribonuclease 7 (RNase 7), and nucleotide-binding oligomerization

Table 1. Studies involving genetic/genomic alteration in patients with HS

Study	Methods	Main results
Theut Riis, P.[23]	Whole-exome sequencing and Mendelian analysis of 11 families with HS from Denmark.	- Mutation in the Notch pathway for all families. - Mutation in *PSENEN* and *APH1B* was found. - A causative mutation for each family was not found.
Vural, S.[13]	Sanger sequencing of all exons and exon-intron boundaries of GSC genes in 38 patients with clinically diagnosed HS.	- GSC gene mutations were detected in 3.2% of individuals with HS - Logarithm of odds never exceed 1.5: multi-genic inheritance pattern within the affected family.
Giatrakos, S.[18]	Sanger sequencing of *IL12RB1*: 139 patients and 114 healthy controls.	- No significant differences between genotype and allele frequencies between the two groups. - H1 haplotype (major frequency alleles in the studied SNPs) was associated with late-onset disease. - H2 haplotype (minor frequency alleles in the studied SNPs) was associated with a greater risk of the acquisition of Hurley III disease stage and with the involvement of a greater number of skin areas.
Giamarellos-Bourboulis, E.J.[19]	Copy number variations of *DEFB* 163 patients with HS and 185 healthy control subjects from Greece; 98 patients with HS and 329 healthy control subjects from Germany.	- Copy number was high in patients compared with controls: more than six copies were associated with a 7.53 odds ratio for HS in the Greek cohort and 5.76 odds ratio for HS in the German cohort. - Fewer than six copies of the gene were associated with earlier onset disease, less frequent presentation of skin lesions with permanent purulent discharge, and fewer affected skin areas.
Dany, M.[20]	Gene expression of enzymes involved in sphingolipid metabolic pathway in inflammatory skin lesions from 17 HS patients and 13 clinically healthy skin subjects.	HS patients had decreased expression of enzymes generating ceramide and sphingomyelin, and increased expression of enzymes catabolizing ceramide to sphingosine and of those converting ceramide to galactosylceramide and gangliosides.
Hessam, S.[21]	Expression of DNA hydroxymethylation regulators: TET and IDH family in 20 patients with HS (lesional and perilesional tissue) and 12 healthy subjects.	All genes were under-expressed in lesional HS skin. Some of them were also under-expressed in perilesional skin.
He, Y.[24]	Relation between *NCSTN* mutations and miRNA microarray expression in five familial HS patients.	*NCSTN* mutations lead to decreased miR-30a-3p levels impacting the RAB31/EGFR signaling pathway.
Rumberger, B.E.[25]	Expression of 114 genes in the skin of 34 patients with mild to severe HS and 16 healthy subjects.	129 genes were upregulated in HS skin and associated with immune activation. It includes pro-inflammatory cytokines, IL-17-associated cytokines, IL-10 family of cytokines, and IFN family members.
Zouboulis, C.C.[26]	Whole transcriptome profile of apocrine glands isolated from skin biopsies of involved and uninvolved skin of 16 HS patients.	*SULF1* is upregulated in the apocrine glands of all patients. The expression of other genes seemed to be gender-dependent.
Hessam, S.[27]	NCSTN, Notch1-3, PIK3R, and AKT mRNA and protein expression in healthy controls and lesional/perilesional skin of patients with HS.	All the studied genes are overexpressed in HS lesions. Gene expression in perilesional skin is associated with disease severity.
Ocejo-Vinyals, J.G.[22]	HLA allele distribution in 106 HS patients and 262 healthy controls from a Caucasian population.	HLA-II alleles (DRB1*07, DQA1*02, DQB1*02, and DQB1*03:01) and the DRB1*07~DQA1*02~DQB1*02 haplotype could influence resistance or susceptibility to HS

TET: ten-eleven translocation; IDH: isocitrate dehydrogenase; IFN: interferon; IL: interleukin; SULF1: sulfatase 1; HLA: human leukocyte antigen system; SNPs: single nucleotide polymorphisms.

domain-containing (NOD2)[31] in lesional and non-lesional skin[32]. Cathelicidin immunoreactivity was significantly increased both in HS epidermis and dermis, along with TNFα. This raises the question of whether the secretion of AMP by the skin could amplify cytokine production (and therefore inflammation), thus facilitating/promoting HS development[33]. Furthermore, the elevated levels of cathelicidin in HS lesions were correlated with the presence of a Th1/Th17 immune response[39].

On the contrary, decreased expression of innate defense AMP was shown in hair follicles, namely the deficient production of RNase 7 and reduced

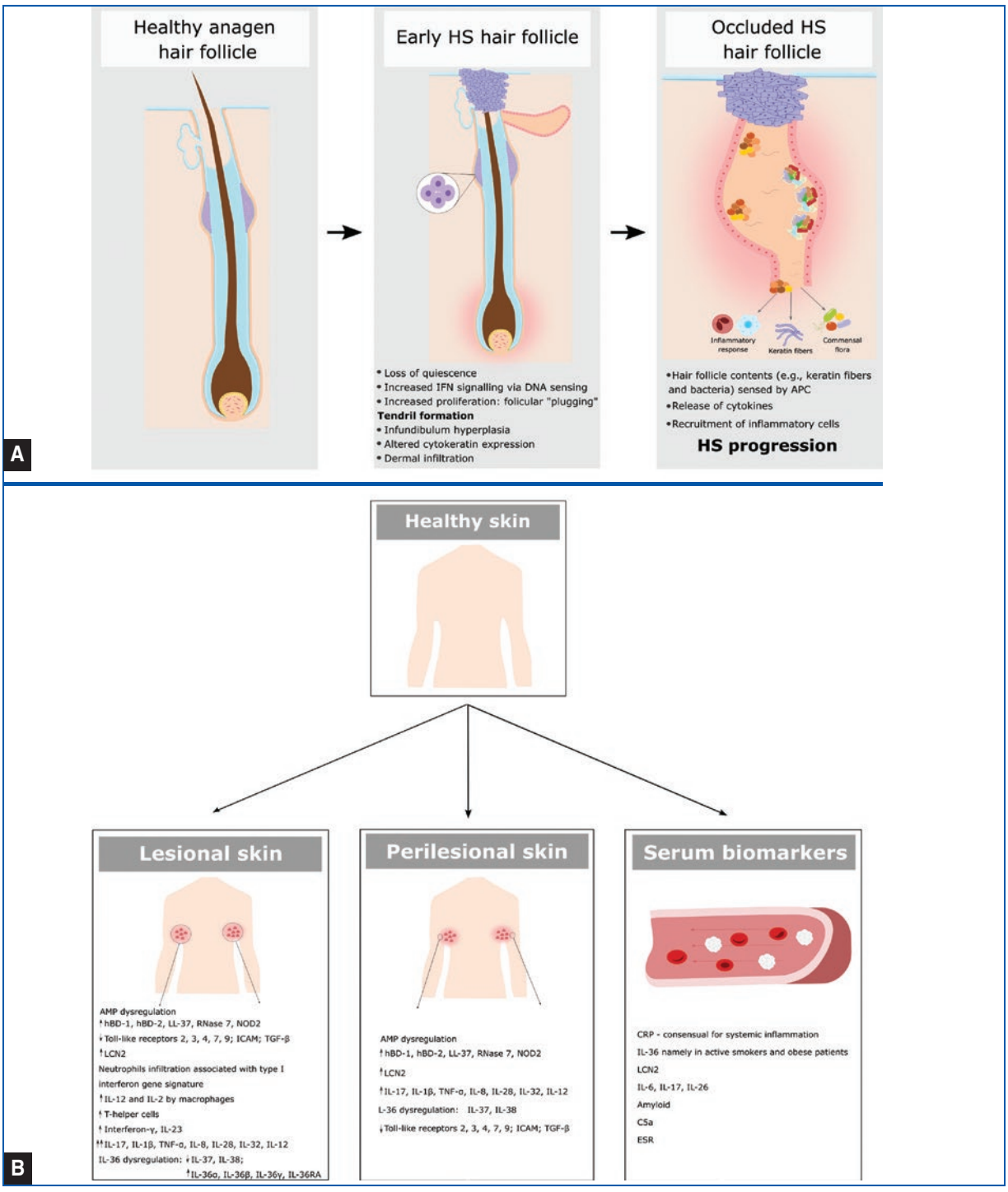

Figure 3. Initial events of HS and the contribution of the immune system to the pathophysiology of the disease. **A:** initial events of HS: The initial pathophysiology of HS is related to alterations of the infundibular epithelium that lead to follicular "plugging" and subsequent stasis of follicular content, propagation of resident bacteria, and dilation of the hair follicle unit[3-6]. IFN: interferon; DNA: deoxyribonucleic acid; APC: antigen-presenting cells. **B:** changes in immune system components in lesional, perilesional skin, and serum in HS patients. There is a dysregulation of AMP mechanisms contributing to the development of HS. Both innate and adaptive immune systems are involved in the HS process, with upregulation of pro-inflammatory cytokines in both lesional and perilesional skin. There is some evidence concerning up-regulation of serum biomarkers. Nevertheless, only high levels of C-reactive protein are consistent among patients with HS[28-42]. AMP: antimicrobial peptides; hBD: human-β-defensin; LL-37: cathelicidin; RNAase 7; ribonuclease 7; NOD2: nucleotide-binding oligomerization domain-containing 2; ICAM: intercellular adhesion molecule; TGFβ: tumor growth factor β; IL: interleukin; CRP: C-reactive protein; LCN2: lipocalin 2; c5a: complement factor C5a; ESR: erythrocyte sedimentation rate.

hBD-3 induction, which could also contribute to inflammation and HS severity[35]. High levels of lipocalin-2 (LCN2) were detected in serum and lesional skin from HS patients as a consequence of granulocyte and keratinocyte response to TNFα[36]. TNFα overproduction is also stimulated by complement factor C5a, which is activated in HS patients and may be used as a surrogate biomarker for HS[43]. Furthermore, complement factors C3a and C5a are associated with NLRP3 inflammasome, a driver of inflammation in HS[44]. Another study evaluating the presence of innate immunity markers in lesional and non-lesional skin (such as toll-like receptors 2, 3, 4, 7, and 9, intracellular adhesion molecule 1, IL-6, IL-10, TNFα, melanocyte-stimulating hormone, TGFβ, β-defensin 2 and 4, and IGF), showed a significantly decreased expression of all markers, with the exception of IL-10. Moreover, this downregulation was more pronounced in lesional skin compared to normal skin, except for TNFα[45]. Leukocyte populations seem to be dynamic in HS: in early-stage HS lesions, plasma cells are predominant, whereas in late stages, the main players are granulocytes[46].

Different studies tried to identify a cytokine profile in lesional, perilesional, and healthy skin. The IL-23/Th17 pathway has been recurrently evaluated in HS due to its important role in promoting excessive tissue inflammation. Tissue samples from lesional HS skin, compared with healthy skin, showed that IL-12 and IL-23 were abundantly expressed by macrophages infiltrating papillary and reticular dermis. Moreover, IL-17-producing T-helper cells, which are important sources of proinflammatory cytokines, were also found more often in lesional HS dermis than in healthy controls' skin[37,38,47]. Treatment with anti-TNFα drugs induces a significant reduction of cutaneous Th17 cells and was shown to balance the immune dysregulation of HS[38]. Further studies have associated the Th1/Th17 axis with the inflammatory profile of HS skin, namely through the demonstration of clustering of IL-17, interferon (IFN)—IFN-ϒ, IL-12, IL-23, IL-32, IL-1β, and TNF in lesional skin[34]. A marked upregulation of IL-17 was found in perilesional and lesional HS skin, characterized by high expression of LCN2 and high inflammatory burden[40]. A recently published study, using RNA sequencing and immunohistochemistry analysis, showed a transcriptomic and molecular profile of perilesional HS skin comparable to lesional HS skin, specifically concerning cluster of differentiation (CD)—$CD3^+$, $CD11C^+$, and neutrophil elastase-positive cellular infiltration, together with a marked upregulation of IL-17. Furthermore, the molecular levels of LCN2 could be used to group HS into two distinct subtypes: LCN2-high HS and LCN2-low HS; the former exhibits an overall higher inflammatory burden and upregulation of targetable cytokine genes, namely IFN-ϒ, IL-6, IL-1B, TNF, and colony-stimulating factor 3[40].

The levels of pro-inflammatory cytokines IL-1β, TNFα, IL-8, IL-28, IL-32, IL-23, the anti-inflammatory cytokine IL-10, and IL-6 (with both pro-inflammatory and anti-inflammatory roles) were also raised in HS lesional and perilesional skin, showing a positive correlation with disease severity[28,30,32,48-51]. This presence of pro-inflammatory cytokines beyond HS lesions could explain the high recurrence rates after surgical excision, highlighting the importance of systemic inflammation in the progression of the disease. In wound exudate samples collected from eight HS patients, IFN-ϒ levels were also significantly elevated compared to chronic wounds, demonstrating a significant inflammation[52]. IL-36 family was also dysregulated in HS lesions and perilesional skin. Interestingly, although IL-36α, IL-36β, IL-36ϒ, and IL-36Ra were overexpressed in lesional HS skin compared with healthy controls, IL-37 and IL-38 were overexpressed in perilesional skin but downregulated in lesional skin[53].

Other members of the TNF superfamily, CD27, and OX40, are preferentially expressed by skin resident regulatory T cells. Under inflammatory conditions, CD27 and OX40 lack the capacity to suppress Th17-associated genes, increasing the production of IL-17 in the skin of patients with psoriasis and HS[54].

Mesenchymal stem cells can be isolated from different tissues, including skin. There is some evidence of their involvement in the early phase of HS development. Mesenchymal stem cells isolated from the skin of 11 patients with HS exhibited elevated levels of T-cell cytokines, namely, IL-6, IL-10, IL-12, IL 17A, TNFα, TGFβ, and IFN-ϒ, showing an immune dysregulation[55]. Hair follicle stem cells and, more precisely, the outer root sheath cells isolated from HS patients had increased proliferation of progenitor cells, losing quiescent stem cells and leading to the production of type I IFNs and skin inflammation[56].

Besides inflammatory markers in lesional and perilesional HS skin, serum inflammatory markers such as IL-6, IL-17, IL-26, IL-36, C-reactive protein (CRP), serum amyloid, C5a, and erythrocyte sedimentation rate are increased in HS patients. These were pointed out as possible biomarkers of HS severity and systemic inflammatory burden[41,44,57-61]. However, this is not consensual: one recent study did not find significant differences in TNFα, IL-1β, IL-17A, or IL-23 in the serum of

HS patients; only high-sensitivity CRP (hs-CRP) can be used as an indicator of systemic inflammation[42,62].

Interleukin-36 levels were significantly higher in patients with HS who actively smoked or presented with obesity or metabolic syndrome[61].

Contrary to other cytokines, the levels of IL-22 are decreased in patients with HS and do not correlate with inflammatory status or disease severity[63]. The role of the IL-22 pathway in HS was assessed in vitro using HS keratinocytes that exhibited significantly lower levels of IL-22 compared with normal keratinocytes[64].

A comprehensive understanding of B-cells in the pathogenesis of many skin diseases, including HS, is scarce[65,66]. Some evidence shows the production of antibodies by B-cells in HS, such as IgG, IgM, anti-*Saccharomyces cerevisiae* antibodies, and aspartoacylase antibody, that could be novel biomarkers for disease severity[67]. There are also some clues demonstrating that B-cells can indirectly increase cytokine production, namely IL-10 and IL-35, and complement activation, with Bruton´s tyrosine kinase and spleen tyrosine kinase pathway activation that work as a central signal transduction network in HS, amplifying the pre-existing inflammatory response interacting with T-cells[65,67]. Despite all this data, the actual role of B-cells in HS remains unclear[65,67].

Microbiome

Evidence that implicates the involvement of the cutaneous microbiome in HS pathogenesis is recent, albeit the association between HS and bacteria has been suggested in the first reports on the disease. Microbial colonization of HS lesions has been investigated in different studies, and most patients were found to be positive for bacterial colonization[4,68,69]. Several studies reported an array of bacterial specimens sporadically isolated from lesional HS skin or exudate using traditional cultural methods. Research based on the most recent next-generation genome sequencing supports that HS patients have a distinctive skin microbiome. The evidence from traditional cultural methods and next-generation sequencing are summarized in Table 2. Bacterial colonization is significantly different in HS inflammatory lesions, HS tunnels, nonlesional HS skin, and people without HS[70].

The microbiome of HS lesions comprises predominantly aerobic bacteria such as *Corynebacterium* and anaerobes such as *Porphyromonas* spp. and *Peptoniphilus*[78]. *Acinetobacter* and *Moraxella*[71] are the main bacterial specimens found on nonlesional skin of HS patients, while *Propionibacterium* spp. and *Staphylococcus* epidermidis are skin commensals prevailing in healthy adults[71]. The anaerobic bacteria *Porphyromonas* spp. and *Prevotella* spp. were associated with HS tunnels[69].

Data concerning the presence of *Staphylococcus aureus* on HS skin are contradictory since some studies report it and others do not[4,68]. On the other hand, the carriage status of S. aureus on nasal and oropharyngeal mucosa was observed in 25% of HS patients with a prevalence of 35.3% of methicillin-resistant S. aureus (MRSA) associated with Hurley stage III[72].

Additionally, bacterial biofilms seem to have a key role in promoting inflammation and breaking the innate skin barrier[73-75]. Bacterial biofilms are found in 67%-75% of sinus tracts and infundibula and are larger in HS lesions than in perilesional skin[75]. However, in a case-control study, fewer bacteria aggregates and biofilms were detected in clinically unaffected axillary HS skin compared to healthy skin[76]. Besides these results, the bacterial composition of HS patients´ peripheral blood did not differ from healthy controls[77].

Finally, the skin-gut axis microbiome alpha diversity seemed to be lower in patients with HS. The authors speculated that this finding could be related either to disease pathophysiology or antibiotic usage[78].

Endocrinology

The association between HS and metabolic syndrome has been suggested in several studies[79-83]. Metabolic syndrome includes diabetes mellitus, hypertension, dyslipidemia, and obesity and is linked to chronic inflammation. Studies correlating obesity and HS will be further explored in the risk factors section chapter.

Thyroid hormones play a central role in metabolism, exerting pleiotropic effects on the metabolism of glucose and lipids and, consequently, on adipogenesis[84]. Therefore, their role in HS has also been addressed. Nevertheless, although thyroid disease seems to be associated with HS severity, data is not consensual concerning the impact of decreased or increased thyroid function on HS (Table 3)[84-86].

Like metabolic syndrome and thyroid function, polycystic ovarian syndrome (PCOS) has also been linked to HS, although the evidence is limited[87]. PCOS has a high comorbidity burden, and there is some overlap with HS endocrine comorbidities, such as obesity, diabetes mellitus, and metabolic syndrome[87]. Table 3 summarizes the different studies associating endocrine conditions with HS.

Table 2. Studies on the skin microbiome in HS patients

Study	Methods	Main results
Jahns, A.C.[4]	Retrospective study including archival skin appendage samples of 27 HS patients. Immunofluorescence labeling with monoclonal and polyclonal antibodies against gram-positive bacteria: Propionibacterium acnes and Propionibacterium granulosum. Fluorescence in situ hybridization for *Staphylococcus* spp. identification.	– 56% of HS patients had bacterial colonization in hair follicles and/or sinus/tract. – Most identified bacteria: coccoids (71% of the patients) in the form of biofilms and microcolonies. – *S. aureus* and coagulase-negative staphylococci were not detected in any sample.
Katoulis, A.C.[68]	Percutaneous needle aspiration of 22 HS lesions (22 patients). The collected material was cultured in aerobic and anaerobic conditions, and sensitivity tests were performed.	– 68% of the patients were culture positive. – Aerobic bacteria were present in 86% of the samples: *Proteus mirabilis*, *S. haemolyticus*, and *S. lugdunensis*. – Anaerobic bacteria were isolated in 7% of the samples: *Dermacoccus nishinomiyaensis* and *Propionibacterium granulosum*.
Guet-Revillet, H.[70]	65 adult HS patients: cultured 149 lesional skinfold samples and 175 unaffected skinfold control samples. Microbiome of 80 anaerobic lesions was compared to 88 control samples Next-generation sequencing 16S ribosomal RNA gene.	– Anaerobic bacterial cultures were detected in 83% of lesions versus 53% in controls. – Streptococci and actinomycetes were also detected in 33% lesional samples versus 26% in controls. – Next-generation sequencing identified 43 taxa associated with HS lesions: – *Prevotella* spp. and *Porphyromonas* were predominant (rare on healthy skinfolds) contrasting with a reduced population of aerobic commensals – *Prevotella* spp. and *Porphyromonas* were associated with lesional skin independently of gender, duration, and familial history of HS; – Fusobacterium and Parvimonas correlated with clinical severity of HS.
Ring, H.C.[71]	A case-control study (30 HS patients and 24 healthy controls): punch biopsy specimens from patients with HS (lesional and nonlesional) and healthy controls. Next-generation sequencing targeting 16S and 18S ribosomal RNA.	– Microbiome on lesional and nonlesional HS skin differs significantly from that in healthy controls. – Five microbiome types were identified: *Corynebacterium* species (type I); *Acinetobacter* and *Moraxella* species (type II), *S. epidermidis* (types III); *Porphyromonas* and *Peptoniphilus* species (type IV), and *Propionibacterium acnes* (type V). – In lesional skin: type I or type IV predominate. – Health controls: type IV not detected. – *Propionibacterium*: more abundant in healthy controls vs HS skin.
Ring, H.C.[76]	Case-control study (24 HS patients and 24 healthy controls) to investigate the morphology of the axillary skin microbiota by peptide nucleic acid–fluorescence in situ hybridization probes in combination with confocal laser scanning microscopy.	– In healthy controls, bacterial aggregates were found in 92% of the samples: hair follicle (64%) or at the stratum corneum (36%). The identified microorganisms were 92% cocci, 8% rods, and 35% coagulase-negative staphylococci. – In preclinical HS only three samples were positive for small cocci bacterial aggregates.
Ring, H.C.[75]	Biopsies from 42 consecutive patients with HS and chronic lesions: lesional and perilesional skin. Peptide nucleic acid-fluorescence *in situ* hybridization in combination with confocal laser scanning microscopy. Corresponding histopathological analysis on hematoxylin and eosin slides.	– Biofilms were seen in 67% of lesional samples and 75% of perilesional samples. – The mean diameter of aggregates was larger in lesional skin than in perilesional skin. – Large biofilms were mostly situated in sinus tracts (63%) or the infundibulum (37%). – Most sinus tract samples (73%) contained active bacteria that were associated with inflammation. – Abundant keratinous debris may promote biofilm formation by commensal cocci in chronic HS lesions.
Benzecry, V.[73]	A total of 46 patients with HS presented purulent or seropurulent discharge. A total of 60 samples were collected using swabs (deeply introduced in the lesions).	– 52% of the cultures were positive. – 15 bacterial species were isolated. – More prevalent species: *Proteus mirabilis* and *S. aureus*. – Positive cultures correlated with disease severity.

(continues)

Table 2. Studies on the skin microbiome in HS patients *(continued)*

Study	Methods	Main results
Ring, H.C.[77]	Case-control study: identification of bacteria in the blood of 27 moderate to severe HS patients and 26 healthy controls. Next-generation 16S ribosomal RNA gene sequencing and routine aerobic and anaerobic blood culture.	– The identification of bacterial specimens in moderate to severe HS patients' blood did not differ from healthy controls.
Ardon, C.B.[74]	Skin biopsies from active HS (inflammatory nodules and/or sinuses) and noninvolved skin from 26 patients. Specimens were cultured under optimal microbiological conditions for 24h.	– 62% of the HS patients were colonized by *S. epidermis*. – 27 different isolates from S. epidermis were identified: 59% in noninvolved skin and 41% in HS lesions. – All bacterial strains showed planktonic growth and 89% of the isolates were strong biofilm producers, *in vitro*.
Ring, H.C.[69]	Exploratory study in 32 HS patients with tunnels (17 in the groin and 15 in the axilla). Next-generation 16S ribosomal RNA gene sequencing.	– Five microbiome types were identified: *Porphyromonas* spp. (type I), *Corynebacterium* spp., (type II), *Staphylococcus* spp., (type III), *Prevotella* spp., (type IV), and *Acinetobacter* spp. (type V). – Type I and type IV (anaerobic bacteria) were the most frequent genera found in tunnels.
Katoulis, A.[72]	Observational cohort study with 68 consecutive HS patients that had not received any antibiotic therapy during the previous 3 months. Nasal and oropharyngeal sampling.	– *S. aureus* carriage was detected in 25% of the patients. – 35.3% of those had MRSA strains.
McCarty, S.[78]	Case-control study: 59 patients with HS (fecal samples, nasal, and skin swabs of affected sites) and 50 healthy controls (20 nasal and skin swabs; 30 fecal samples). Bacterial 16S rRNA gene amplicon sequencing on total DNA.	– Microbiome alpha diversity was significantly lower in the fecal, skin, and nasal samples of HS patients. – *Ruminococcus gnavus* was more abundant in the fecal microbiome of HS patients. – *Finegoldia magna* was overabundant in HS skin samples relative to healthy controls.

Risk factors

Smoking and obesity are the main risk factors identified for HS[2,85,86,94-101]. A Portuguese retrospective observational study including hospitalized patients who have been diagnosed with HS in the past five or more years showed that the most common risk factor was tobacco smoking, observed in 13.6% of the included patients[2]. In a demographically heterogeneous population-based retrospective analysis in the United States, including 7860 patients with HS, the incidence of HS among tobacco smokers is approximate twice the observed among nonsmokers[95].

A study based on questionnaires reporting the data of 129 patients diagnosed with HS, with a median follow-up of 22 years, showed that 92.2% of the patients were smokers and that among nonsmokers, 40% reported disease remission compared with 29% of active smokers. Concerning obesity, remission was reported in 45% of nonobese patients compared with 23% of obese patients[94]. Nevertheless, the role of tobacco use and body mass index (BMI) seemed to be less frequently associated with early-onset disease (≤ 17 years old)[102].

Data on early-onset disease are very limited. In a study on 134 patients, disease onset during adolescence occurred in 51.5% and was associated with female sex, family history of HS, presence of pilonidal sinus, acne conglobata, longer disease duration, and worse perception of disease severity[103]. These are important factors for the identification of individuals at high risk of early-onset and more severe disease.

The factors that determine the involvement of different skin areas in HS are not well understood. A French study based on a multivariate regression analysis of data collected from 1138 patients concluded that patients' characteristics (sex, age, BMI, family history, and smoking status), disease features (severity and other sites affected by HS), and comorbidities (arthritis, inflammatory bowel disease, acne vulgaris, acne conglobata, pilonidal disease, and dissecting folliculitis of the scalp) correlated with affected sites[104]. Two other studies, carried out in Argentina and Turkey, concluded that perianal and gluteal lesions were associated with higher HS severity, as well as male gender[96,97].

Different comorbidities have been linked to HS and could complicate the course of the disease[85,86,96,97,105-111]. Comprehensive analysis showed that the main comorbi-

dities associated with HS were acne, polycystic ovary syndrome, pilonidal sinus, metabolic syndrome, autoimmune disease, and mental health disorders[110].

Pilonidal sinus is a fistulating chronic inflammation affecting the sacrococcygeal region, which shares common histological, immunohistochemical, and ultrasound features with HS[105,109]. Moreover, solitary intergluteal HS lesions are similar to pilonidal sinus, and there is a lack of evidence confirming if they represent a spectrum of the same disease or two different entities[109]. A multicentric, cross-sectional study reported intergluteal fold lesions in approximately one-fourth of the patients with HS. Of these patients, pilonidal sinus disease was confirmed afterward in 78% of the cases. In patients in whom HS was confirmed, the lesions were associated with the proximity of the intergluteal fold, including the buttocks, genitals, and anus. Furthermore, this clinical phenotype occurs predominantly in men, at younger age, smokers, with a family history of pilonidal disease, and is associated with higher recurrence rates and severity[109]. HS, pilonidal sinus, acne conglobata, and dissecting cellulitis are diseases of the follicular occlusion tetrad[112].

Although literature reporting the relationship between acne conglobata and HS is limited[103,104], it has been associated with a higher risk of early disease onset[103] and correlated with the involvement of the sub-gluteal localization of HS[104].

Another condition that shares many aspects, namely clinical, dermatoscopic, pathogenetic, and histologic aspects with HS, is dissecting cellulitis of the scalp (DCS)[112]. HS, sinus, acne conglobata, and DCS are diseases of the follicular occlusion tetrad[112]. The prevalence of DCS among patients diagnosed with HS varies between 1-8%[97,103]. In both diseases occurs scalp perifolliculitis, and therefore some authors defend that DCS and HS should be considered the same disease affecting different localizations: scalp and apocrine gland-rich areas of the skin, respectively[97,103,112]. The likelihood of developing HS was also assessed in patients with acne vulgaris, with the association being stronger for men over 65-year-old[113]. In an Israeli population, a cross-sectional study also showed an association between acne keloidalis nuchae and HS. However, further observational studies are needed to confirm this relationship[114].

The coexistence of HS and atopic dermatitis was also demonstrated in a population-based retrospective study that included 6779 patients with HS[115]. Patients with HS were twice likely to develop atopic dermatitis compared with a control population[115]. Patients diagnosed with both diseases were predominantly female, nonsmokers, and nonobese[115]. Recently, an association between psoriasis and HS has also been addressed and demonstrated in two large-scale studies[116,117]. A study with 68,836 patients with psoriasis and the same number of healthy controls showed that the prevalence of HS is increased in patients with psoriasis. Furthermore, the coexistence of the two conditions occurred predominantly in younger patients with a higher prevalence of obesity and smoking.[117] The co-occurrence of psoriasis and HS was explored in a Danish study: HS patients had an OR of 2.99 (95% confidence interval (CI) 2.04-4.38) for having psoriasis, compared with healthy controls; on the other hand, psoriasis patients had an OR of 2.56 (95% CI 1.74-3.77) of having HS. This study showed a strong association between the two conditions[116].

The predisposition to develop HS was evaluated in patients with inflammatory bowel disease (IBD), showing that both diseases can coexist in the same patient[106,107,111,118]. A population-based study demonstrated that patients with IBD, including Crohn´s disease (CD), and ulcerative colitis, have a 9 fold higher risk of developing HS compared to the general population, particularly in females[107]. On the other hand, the predisposition to develop CD in patients with HS was also addressed in a population-based analysis in the United States[108]: patients with HS are at high risk of developing CD, approximately 3 times more likely. This association was stronger for men aged between 45 and 64 years, nonsmokers, and with perianal disease[108,111].

Stress mechanics, namely friction and skin trauma, were associated with HS based on the Koebner phenomenon. This seems to be especially relevant in obese patients[119].

Some exploratory studies tried to find biomarkers that could be considered risk factors for the development and severity of HS[120,121]: HS patients had significantly higher retinol-binding protein 4 and lower ghrelin levels, associated with an increased risk of HS[120]; an atherogenic index of plasma ≥ 0.11 was significantly and independently associated with the severity of HS[121].

Discussion

The precise pathophysiology of HS is not fully understood. In this systematic review, five main contributors to HS pathophysiology were addressed: genetics, immunity, microbiome, and endocrinology, together with the identification of risk factors/comorbidities. Mutations in genes encoding gamma-secretase, an intramembrane protease complex, are among the most commonly

Table 3. Studies reporting endocrine-related conditions in HS patients

Study	Methods	Main Results
Metabolic Syndrome		
Sabat, R.[79]	A hospital-based case-control study in 80 HS patients and 100 age- and sex-matched control patients.	– HS patients have a high prevalence of metabolic syndrome. – Role of metabolic alterations in the development of HS: central obesity (OR for HS development: 5.88); hypertriglyceridemia (OR for HS development: 2.24); HDL-cholesterolemia (OR for HS development 4.64); hyperglycemia (OR for HS development 4.09).
Gold, D.A.[80]	Retrospective chart review of 366 patient files.	– The prevalence of metabolic syndrome was 50.6% in HS patients and 30.2% in the control group ($p < 0.001$).
Miller, I.M.[81]	Cross-sectional population- and hospital-based study of HS and metabolic syndrome.	– HS appears to be associated with metabolic syndrome – Causality remains to be explored.
Shalom, G[82]	Cross-sectional study in 3297 patients with HS and 6412 age- and sex-matched control patients without HS.	– Association between HS and diabetes, hyperlipidemia, obesity, hypertension, and metabolic syndrome in HS.
Miller, I.M.[88]	Cross-sectional study in both hospital-based and population-based HS and control groups using Bioelectrical Impedance analysis to assess body composition.	– Age and sex-adjusted analysis showed a higher predicted estimated basal metabolic rate in HS patients that reflects a dysfunctional metabolism.
Vossen, A.[83]	Hospital-based cross-sectional study to classify body types (waist circumference and waist-to-hip ratio in 106 HS patients and 212 healthy controls.	– Waist-to-hip ratio did not differ in the HS group compared with the control. – A peripheral pattern of body weight distribution was seen more frequently in the HS group.
Akdogan, N.[89]	Case-control study with 40 HS patients and age- and gender-matched controls to study obesity, adipokine imbalance, dyslipidemia, pro-inflammation, and metabolic syndrome.	– HS patients have higher serum visfatin, insulin and hs-CRP levels, independent of BMI and smoking status, which are risk factors.
Jorgensen, A.R.[90]	Cohort study included 34,7200 school children that could receive a diagnosis of HS in the follow-up.	– Childhood BMI was positively and significantly associated with the risk of HS development in adulthoods.
Reichert, B.[91]	Retrospective chart view of 535 pediatric HS patients.	– 54.2% were obese and 11.6% were overweight.
Barrea, L.[92]	35 treatment-naïve HS patients and 35 controls matched for sex, age, and BMI.	– Circulating trimethylamine N-oxide positively correlated with HS Sartorius score, being a predictor of HS clinical severity.
Wright, S.[93]	Retrospective case-control analysis of 1284 patients with HS and controls matched for age, sex, and race.	– The influence of BMI may play a larger role among female and younger patients.
Polycystic ovary syndrome		
Garg, A.[87]	Cross-sectional analysis involving 22,990 patients with HS in the United States.	– Prevalence of PCOS is 9.0% among patients with HS and 2.9% in patients without the disease. – The likelihood of having PCOS in HS patients was 214 times higher than in patients without HS. – The strength of the association between HS and PCOS was similar to that of diabetes mellitus and obesity with PCOS. – A causal link could not be established.
Thyroid disease		
Miller, I.M.[84]	Retrospective comparative cross-sectional study, a population-based study compared with a control group.	– Significantly lower levels of TSH and significantly higher levels of T3 were detected in HS patients compared with the control group – HS is associated with hyperthyroidism.
Liakou, A.I.[85]	Prospective cross-sectional study with 290 patients with HS.	– Thyroid disease was associated with a higher stage of the disease.
Sherman, S.[86]	Cross-sectional population-based study including 4191 HS patients and 20,941 controls.	– HS is independently associated with hypothyroidism. – Hyperthyroidism is associated with HS only in females, middle-aged patients, and nonsmokers.

BMI: body mass index; PCO: polycystic ovary syndrome; OR: odds ratio; TSH: thyroid-stimulating hormone; T3: triiodothyronine; hs-CRP: high-sensitivity C-reactive protein.

described mutations in HS patients[8,13]. However, while up to 30-40% of patients have a positive family history of HS, only a small subset harbor genetic variants in components of the gamma-secretase complex[15]. GSC is responsible for the cleavage of several transmembrane proteins[16], and mutations in this complex result in dysregulation of Notch signaling[14]. Attenuation of Notch signaling is responsible for keratinocyte hyperplasia in the follicular infundibulum and also for changes in cytokine production by T cells[122]. However, in more than 90% of HS patients, the genetic features contributing to disease development remain largely unknown. Furthermore, the identified GSC mutations have not been found in sporadic cases of HS, which is the most common presentation. So, it is clear that efforts should be made in order to identify genetic polymorphisms that increase susceptibility to the disease, perhaps through wide genome association studies. This could improve our comprehension of HS phenotypes and disease prognosis and, together with a better understanding of immunopathogenesis, lead to the development of tailored treatments.

Hidradenitis suppurativa is characterized by inappropriate AMP secretion, and proinflammatory cytokine dysregulation[29,30,32,35]. Increased activity of dendritic cells and T cells cause keratinocyte hyperplasia via IL-23, IL-12, and Th17 immune response[30,47]. As HS progresses, increased levels of IL-1, TNF, IL-17, caspase-1, and IL-10 appear in tissue together with the recruitment of neutrophils, mast cells, and monocytes[28]. Neutrophils attracted by the IL-1-induced chemokines contribute to inflammatory cytokines production and pus formation[37,43]. LCN2 is one of the cytokines produced by neutrophils that cause inflammatory pain, and further neutrophil tissue infiltration[36,39,40]. The development of sinus tracts and scarring is associated with metalloproteinase-2, transforming growth factor beta and intercellular adhesion molecule-1[30]. Regarding serum biomarkers, only CRP has been consistently correlated with clinical inflammation in HS patients[41,42].

There is recent evidence implicating the involvement of skin microbiota in HS pathogenesis[68,69,71,72,75-77]. In HS lesional skin and nonlesional skin, there is an imbalance of skin microbiota with a predominance of anaerobes and cocci/coccobacilli bacteria[70,76]. However, there is a lack of consensus regarding which bacteria species are the most common[4,68,70,72]. In addition to the characteristic dysbiosis in HS, biofilm formation is common in HS and contributes to the rupture of the innate skin barrier and to local and systemic inflammation[74,75]. Antibiotic treatment is commonly used in HS management. Apart from its antibacterial effect, it has an immunomodulatory action. The role of antibiotic therapy and the risk of resistance induction is not well established and highlights the importance of pondering the benefit versus potential harms of antibiotic therapy in HS.

Patients with HS may be at high risk of metabolic syndrome, and clinicians should be aware of this association and be alert to the different components of metabolic syndrome regardless of the young age of the patients[81-83,94,98]. Although PCOS is associated with HS, further studies are needed to characterize the relationship between the two conditions[87]. Existing data correlating HS with other endocrinopathies, such as thyroid disease, are particularly scarce and contradictory, and a clear association cannot yet be established[84-86].

The role of lifestyle in the development of HS is well established[123,124]. HS is associated with many comorbidities, most of which are inflammatory. Tobacco smoking and obesity are strongly associated with HS[2,85,86,94-101]. Approximately 90% of patients are current or former smokers, and smoking appears to contribute to disease onset and progression[95]. The underlying mechanisms are still not clear, but nicotine is known to promote proinflammatory cytokines, induce epidermal hyperplasia, and interfere with the microbiome[93]. Obesity might contribute to HS pathogenesis through subclinical inflammation, metabolic changes, and friction[99,100].

In conclusion, HS is a chronic, inflammatory, debilitating disorder. HS etiopathogenesis has not been entirely elucidated. This systematic review updated the most recent understanding of HS pathogenesis, integrating inflammatory pathways that include genetics, immunity, endocrinology and microbiome. Other contributing factors identified as HS risk factors and comorbidities were discussed and included in this cohesive multifactorial model. Despite the vast increase in knowledge in the last few years, there is much to unveil in the comprehension of this highly complex and multifactorial disease.

Conflicts of interest

Pedro Mendes Bastos has received honoraria for acting as a consultant and/or as a speaker for AbbVie, Janssen, Novartis, LEO Pharma, Almirall, Sanofi, Viatris, L'Oréal and Cantabria Labs. He has also worked as a principal investigator in clinical trials supported by Pfizer, AbbVie, Sanofi, and Novartis. Joana Cabete has received honoraria for acting as a consultant and/or as a speaker for Novartis and Abbvie. She has worked as investigator

in clinical trials supported by Novartis. The remaining authors have no conflicts of interest to declare.

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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 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.

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REVIEW ARTICLE

Ectodermal dysplasias

Displasias ectodérmicas

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Abstract

Ectodermal dysplasias are a heterogeneous group of rare inherited disorders. Molecular findings and clarification of cell signaling processes and ectodermal-mesenchyme interaction enabled the development of a clinical-functional model, which in turn helps to explain clinical signs, with variability in severity, associated non-ectodermal abnormalities and overlap seen in many patients. We herein review the current state of knowledge regarding this distinct entity and illustrate with an elucidative case report. The need for early multidisciplinary intervention is highlighted, and further studies will focus on genetically-target therapeutic approaches.

Keywords: Ectodermal dysplasia. Genodermatosis. Genetic testing.

Resumo

As displasias ectodérmicas representam um grupo heterogéneo de doenças hereditárias raras. Os achados moleculares e o esclarecimento dos processos de sinalização celular e da interação ectoderme-mesênquima permitiram compreender os sinais clínicos. Estes caracterizam-se por gravidade variável, observando-se associação a anomalias não ectodérmicas e sobreposição clínica em muitos pacientes. No presente trabalho resumimos o estado atual do conhecimento sobre as displasias ectodérmicas e apresentamos ainda um relato de caso ilustrativo. Salientamos a necessidade de intervenção multidisciplinar precoce, sendo necessários estudos futuros com enfoque em abordagens terapêuticas geneticamente direcionadas.

Palavras-chave: Displasia ectodérmica. Genodermatose. Teste genético.

Introduction

The term ectodermal dysplasia (ED) designates a heterogeneous group of rare inherited disorders characterized by abnormal development of ectodermal tissues (hair, nails, sweat glands, and teeth). In addition, non-ectodermically derived structures may also be affected[1]. To date, approximately 200 conditions are described, and the causative mutation has been identified in some cases[2,3]. Clinical knowledge and the unravelling of molecular mechanisms has therefore led to the development of classification systems[4,5].

We herein review the current expertise on this topic, regarding etiology, evaluation and management options, highlighting the importance of multidisciplinary strategies for improved outcomes. We further illustrate with a clinical case.

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Historical perspective

EDs have long been recognized, with the earliest reports dating from 1792 by Danz[6], with subsequent descriptions made by Wedderburn in 1838, Thurnam in 1948[7] and Charles Darwin in 1875[8]. Later on, the term "hereditary ectodermal dysplasia" was introduced by Weech in 1929, who coined as "anhidrotic" those with inability to perspire[9]. In 1944, Felsher further changed the adjective to "hypohidrotic," as these individuals were not truly devoid of sweat glands[2]. Since then, several cases have been reported and disease comprehension originated classification schemes.

Etiology and epidemiology

The word ectoderm comes from the Greek ektos meaning "outside" and derma meaning "skin." Indeed, it represents the outermost primary germ layer, formed in early embryonic development, superficial to the mesoderm (the middle layer) and the endoderm (the innermost layer). At around the third week of development, it differentiates to form neural (neuroectoderm) and epithelial tissues (epidermis, epidermal appendages and tooth enamel). As such, the ectoderm originates not only the hair, teeth, nails and sweat glands, but also the central and peripheral nervous system, eyes, ears and nose, along with the eccrine, mammary and pituitary glands[10]. Moreover, the ectoderm interacts with the mesoderm during development, which explains that abnormalities in mesodermal structures (such as the musculoskeletal and genitourinary system) may feature EDs[5].

ED is thus defined by a congenital defect in at least two of the major ectodermically derived structures (hair, nails, sweat glands, and teeth), and represents single-gene disorders with a variable mode of inheritance[1,2,11]. They result from the mutation or deletion of certain genes located on different chromosomes, responsible for cell signaling processes involved in the induction and development of ectodermal structures and their interactions with the mesoderm. They are usually inherited, but *de novo* mutation is also possible[2,3].

EDs are considered rare conditions, with an estimated incidence of 7:10000 births[12]. Approximately 200 conditions are known. The commonest variant is hypohydrotic ED, which is frequently X-linked with full-blown expression seen only in males[1,2,11].

Genetic pathogenesis[2,3,5]

Biomolecular investigation has enabled the identification of causative mutations, that can be categorized under two broad pathogenic mechanisms (see classification section below)[5]:

Defective interaction between the ectoderm and the mesenchyme

Changes in the signaling pathways that modulate activity of nuclear factor kappa-light-chain-enhancer of activated B cell (NFκB).

EDA/EDAR/EDARADD pathway

The EDA, EDAR and EDARADD genes provide instructions for making proteins that work together during embryonic development. Mutations in these genes result in defective ectodysplasin (EDA) formation, which is critical for the interaction between the ectoderm and the mesoderm. In sum, EDA protein binds to an EDA receptor (EDAR) in the cell membrane. EDAR has an extracellular region, a transmembrane region, and a death domain in its intracellular region. A death domain is a protein interaction module that interacts with the death domains of other proteins and triggers metabolic cascades that are often implicated in regulating apoptosis and inflammation through the NFκB cascade. EDAR death domain binds to the death domain of EDAR-associated death domain (EDARADD)[13].

Finally, certain mutations in the WNT10A gene, whose product is a member of the Wnt signaling pathway (implicated in embryonic development and cell differentiation), have also been implicated in certain forms of ED.

Mutations in only 4 genes (EDA1, EDAR, EDARADD and WNT10A) are responsible for most cases of ED, through improper formation of ectodermal structures, leading to the characteristic features of hypohidrotic ED (Table 1)[14].

NFκB signaling pathway

NFκB is a transcription factor that regulates the expression of multiple genes implicated in immune and inflammatory responses, reaction to stress, cell adhesion, and protection against apoptosis[15]. In most cells, NFκB is kept in an inactive state through cytoplasmic sequestering by the NFκB inhibitory protein (IkB). Several stimuli lead to activation of the cell membrane receptors of the TNF family (such as EDAR). Activation of these receptors leads to degradation of IkB, allowing NFκB translocation to the nucleus and

Table 1. Classic ectodermal dysplasias.

	Hypohidrotic ED	Hypohidrotic ED-immune deficiency	Hidrotic ED	Witkop tooth and nail syndrome
Inheritance (associated gene)	XL (EDA); AD, AR (EDAR > EDARADD)	XL recessive (IKBKG/ NEMO); AD (NFKBIA)	AD (GJB6)	AD (MSX1)
Protein product	Ectodysplasin A; EDAR; EDARADD	NF-κB essential modulator; NF-κB inhibitor- α	Connexin 30	Muscle segment homeobox 1
Scalp hair	Sparse to absent; often lightly pigmented in children	Sparse	Wiry, brittle; patchy alopecia; often lightly pigmented	Normal to thin
Teeth	Hypodontia, conical	Hypodontia, conical	Normal	Hypo- or anodontia of secondary teeth; primary teeth regular or small/ peg-shaped
Sweating	Markedly decreased	Mildly decreased	Normal	Normal
Nails	Normal	Normal	White and small during infancy; thickened, distal separation	Koilonychia improves with age; toenails are worse than fingernails
Other	Characteristic facies; neonates may have collodion-like membrane; eczema common; thick nasal secretions and cerumen; frequent respiratory tract infections	Intertrigo, seborrheic-like dermatitis, erythroderma; colitis; recurrent infections (pyogenic or opportunistic); ↑ IgM and IgA, ↑ IgG; rare osteopetrosis and lymphedema, arthritis, and/or (esp. in AD form) autoimmune cytopenias and endocrinopathy	Stippled palmoplantar keratoderma; the grid-like array of tiny acral papules; blepharitis, conjunctivitis	Prolonged retention of primary teeth

AD: autosomal dominant; AR: autosomal recessive; ED: ectodermal dysplasia; EDAR: ectodysplasin A receptor; EDARADD: EDAR-associated death domain; GJB6: gap junction β6; IKBKG: inhibitor of κ light polypeptide gene enhancer in B cells, kinase γ; XL: X-linked. Adapted from H. Itin et al.[1].

culminating in inflammatory and immune responses with development of T and B cells, and induction of osteoclast function and growth of epidermal cells[16]. NFκB essential modulator (NEMO) is a subunit of IkB, that if absent impairs NFκB response to stimuli[17]. Mutations in 2 genes, NEMO and IkB (subunits of IkB) have been shown to give rise to a heterogeneous group of genetic disorders that include some forms of ED (X-linked hypohidrotic ED (HED) with immune deficiency; autosomal dominant HED with immunodeficiency; and osteopetrosis, lymphedema and HED with immunodeficiency) (Table 1)[18].

Regulatory changes in transcription and/or expression of genes such as p63

The p63 our TP63 (tumor protein 63) gene encodes the transcription factor protein p63, which is expressed very early during embryogenesis and plays an essential role in inducing epidermal differentiation and proliferation. As such, lack of expression during the early development of ectodermal tissues might block interactions between the epithelium and the mesenchyme, thereby impairing normal morphogenesis[19]. In addition, p63 regulates the expression of P-cadherin, a critical regulator of hair development[20].

The regions of greatest biological importance are the DNA binding domain, the sterile alpha motif (SAM) and the transactivation inhibition domain (TID)[19]. Heterozygous mutations in the p63 gene are responsible for at least 6 different syndromes that combine ED, orofacial clefts, and limb malformations, with a strong genotype-phenotype correlation that is dependent on the location of the p63 mutation (Table 12)[21]. Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome will be further presented in this review (see Clinical Manifestations section).

Abnormal function of a structural protein in the cell membrane

Examples of structural proteins include nectin 1, connexins and plakophilin, whose role in adhesion and cell-cell communication is essential for tissue

homeostasis and cell growth, development and response to stimuli. Clinically, these disorders feature skin abnormalities (such as palmoplantar keratoderma), with or without involvement of highly differentiated epithelia associated with deafness or retinal dystrophy. Hidrotic ED is caused by mutations in connexin 20, and it is characterized by hair loss, nail dystrophy, and palmoplantar keratoderma (Table 1)[22].

Finally, it should be mentioned that some inherited abnormalities limited to one ectodermal structure have a genetic basis related to that of EDs (e.g., hypodontia due to heterozygous WNT10A mutations versus ED syndromes due to biallelic mutations in the same gene), that should nonetheless not be confused with a true ED.

Classification

There have been many classification schemes proposed over the years. The initial descriptive clinical categorization by Pinheiro and Freire-Maia[4] distinguished four primary ED defects:

- ED1: Tri hodysplasia (hair dysplasia)
- ED2: Dental dysplasia
- ED3: Onychodysplasia (nail dysplasia)
- ED4: Dyshidrosis (sweat gland dysplasia)

The ED were then further categorized into eleven subgroups according to the primary defects:

- Subgroup 1-2-3-4
- Subgroup 1-2-3
- Subgroup 1-2-4
- Subgroup 1-2
- Subgroup 1-3
- Subgroup 1-4
- Subgroup 2-3-4
- Subgroup 2-3
- Subgroup 2-4
- Subgroup 3
- Subgroup 4

The complex classification of ED has later evolved in an attempt to integrate clinical and genetic data. In 2009, Priolo[5] established a clinical-functional model, based on the understanding of the processes of cell signaling involved in the induction and development of ectodermal structures as well as their interactions with mesodermal structures. As such, two groups have been defined:

- Group 1: defective epithelial-mesenchymal interaction with a resulting phenotype of hypoplasia or aplasia of structures derived from the ectoderm —considered "pure EDs" without other dermatologic signs nor skeletal anomalities).
- Group 2: altered cell-cell adhesion and communication–regarded as "dermatologic EDs" (featuring skin abnormalities such as palmoplantar keratoderma), with possible involvement of other ectodermal structures or highly differentiated epithelia (e.g., associated with deafness or retinal dystrophy). In this regard, some of the conditions that might be included in this group have not been traditionally thought of as EDs because their recognition and diagnosis are based upon another primary manifestation (keratoderma, ichthyosis, aplasia cutis congenital, or skeletal dysplasia). Indeed, defects in ectodermal appendages should be the major clinical features used to classify and diagnose EDs[1].

In sum, EDs are nowadays distinguished based on the types of ectodermal abnormalities, associated non-ectodermal anomalies, and mode of inheritance, as well as the underlying genetic defect.

Clinical manifestations

ED develops during the first trimester of pregnancy. If severe, they occur before the 6th week of embryonic life, consequently disturbing the normal dentition. After the 8th week, the other ectodermal structures will be affected[2]. Molecular interactions among proteins mutated in EDs and altered common functional pathways will explain many clinical signs, severity variability, associated malformations, and overlap seen in some ED patients. The detailed description of the different types of ED is not under the scope of this paper and has been extensively reviewed elsewhere[1-3]. We will in turn present some key clinical and genetic features of selected classic EDs, which have a known molecular basis and/or prominent cutaneous manifestations (Tables 1 and 2)[1-3].

- Hypohidrotic Ectodermal Dysplasia (HED) (synonyms: Anhidrotic ED, Christ-Siemens-Touraine syndrome)
  HED describes a group of disorders that present with sparse or absent hair, missing or peg-shaped teeth, and decreased ability to sweat. The most common form is X-linked, which also represents the most frequent ED in general, with an incidence of 1 case per 10,0000 births. HED is caused by mutations in the ectodysplasin signal transduction pathway, namely the EDA, with no apparent genotype-phenotype relationship, and great variety among different families and within the same family

Table 2. p63-related ectodermal dysplasia syndromes

Variables	AEC	EEC	Limb–mammary	Adult
Inheritance	AD	AD	AD	AD
Typical TP63 mutations	Missense in SAM domain	Missense in DNA-binding domain	Truncating in C-terminal region	Missense in hotspot at end of DNA-binding domain
Scalp hair	Lightly pigmented, wiry; sparse with patchy alopecia	Lightly pigmented, coarse; may be sparse	Normal	Lightly pigmented, sparse; frontal alopecia
Teeth	Hypodontia, misshapen (e.g., conical) teeth	Hypodontia, enamel hypoplasia	Hypodontia	Hypodontia, small teeth
Sweating	Hypohidrosis in some patients	Usually normal	Hypohidrosis in some patients	Usually normal
Nails	Hyperconvex, thickened or absent	Transverse ridges, pitting	Variable dystrophy	Ridges, pitting
Cleft lip/palate	Almost 100%; palate ± lip	~50%; usually lip + palate	~30%; palate only	None
Digital anomalies	Syndactyly in some patients; rarely ectrodactyly	Ectrodactyly > syndactyly	Ectrodactyly > syndactyly	Ectrodactyly, syndactyly
Skin findings	Neonatal erythroderma; erosive dermatitis, esp. of scalp; flexural reticulated hyperpigmentation	Xerosis, palmoplantar keratoderma	None	Xerosis, photosensitivity, freckling
Other	Ankyloblepharon; lacrimal duct defects; ectopic breast tissue; hypospadias; GER	Lacrimal duct defects; keratopathy, corneal scarring; GU anomalies	Lacrimal duct defects, hypoplastic nipples/ breasts; GU anomalies	Lacrimal duct defects; hypoplastic nipples/breasts

ADULT: acro-dermato-ungual-lacrimal-tooth; AEC: ankyloblepharon-ectodermal defects-cleft lip/palate; EEC: ectrodactyly-ectodermal dysplasia-clefting; GER: gastroesophageal reflux; GU: genitourinary; SAM: sterile alpha motif. Adapted from H. Itin et al.[1]

group. Altered morphogenesis affecting epithelial cells in the developing tooth, hair follicle, and eccrine gland results in aplasia, hypoplasia, or dysplasia of these structures[1-3].

The scalp hair is sparse or absent with light-brown pigmentation. Affected infants have a loss of the skin's thermoregulatory function, clinically present with pyrexia of unknown origin and hyperthermia as early as the first few hours of life, with increased mortality. Furthermore, the skin appears smooth, soft, dry, and thin due to absent eccrine pores with disturbed dermatoglyphes. Atopic dermatitis is a common comorbidity. There might be a characteristic facial dysmorphism, with periorbital wrinkling, sebaceous hyperplasia of the face, saddle nose, fully-everted lips, and prominent frontal bossing. Teeth are reduced in number and usually peg-shaped. Dental caries and loss of dentition can lead to difficulty in feeding. Nails remain unaffected in HED. Other manifestations include recurrent respiratory tract infections (viscous secretions), hoarseness of voice, gastroesophageal reflux, and unilateral or bilateral breast aplasia/hypoplasia[1-3].

The abovementioned features are mainly observed in males, with females ranging from a carrier state to a limited blaschkoid distribution or even a full-blown disease, depending of X-inactivation. In addition, a subset of patients presents with immunodeficiency in the form of hypogammaglobulinemia and autoimmune cytopenias, with identified mutations in the NEMO gene[1-3].

– Hydrotic Ectodermal Dysplasia (synonym: Clouston syndrome)

It is an autosomal dominant condition that is caused by missense mutations in the GJB6 gene, which encodes the connexin 30 protein. The 3 main clinical characteristics are hair loss, nail dystrophy, and palmoplantar keratoderma, with sparing of teeth and eccrine glands. Hair and nail changes manifest in early infancy and progress over time. Namely, atrichia or hypotrichosis with wiry, brittle and pale hair, and frequently patchy alopecia. In addition, sparse eyelashes predispose to recurrent episodes of conjunctivitis and blepharitis. Nails are milky-white, with gradual thickening throughout childhood. Palmo-plantar keratoderma with a cobblestone-like

pattern on the dorsal aspect resulting from the coalescence of eccrine acrosyringia has been reported in several patients, as oral leukoplakia. Facial dysmorphism is not present and general physical development is normal[1-3].

– Ankyloblepharon-Ectodermal Defects-Cleft Lip/Palate (AEC) Syndrome (synonyms: Hay-Wells syndrome, RappHodgkin syndrome)

Heterozygous mutations in the p63 gene are responsible for at least 6 different syndromes that combine ED, orofacial clefts, and limb malformations[21]. AEC syndrome has an autosomal dominant transmission pattern of non-sense mutations in the SAM domain of protein p63, with approximately 100 patients reported to date[23]. Ankyloblepharon, ectodermal defects, and cleft lip/palate make the characteristic clinical triad[1-3].

This disorder is evident at birth. Up to 90% of affected infants show a classic erythrodermic presentation with peeling skin or erosions, which can result in life-threatening infectious complications. The scalp is almost always involved in the form of chronic oozing erosive dermatitis, patchy alopecia, and wiry hair. Some degree of nail dystrophy is typically evident, with hyperconvex and thickened nail plates or anonychia. Sweating may be decreased with heat intolerance. Additional features that differentiate this syndrome include hyper granulation tissue formation, recurrent skin infections, cribriform and stellate scarring of the shoulders and upper trunk, and reticulated pigmentation of the intertriginous areas. Dental abnormalities include hypodontia and misshapen teeth[1-3].

Congenital strands of tissue are observed between the eyelids (ankyloblepharon) in approximately three-quarters of affected individuals, which may lyse spontaneously, even prior to birth, or require surgical correction. Lacrimal duct atresia may occur. Almost all patients with AEC syndrome present with a cleft palate with or without a cleft lip[1-3].

External ear malformation may be observed, leading to recurrent otitis media with secondary conductive hearing loss. In addition, gastroesophageal reflux develops in the majority of AEC patients, and in some cases results in failure to thrive and requirement of gastrostomy placement. Finally, hypospadias, supernumerary nipples, and limb abnormalities are other associated traits[1-3].

Regarding differential diagnosis, neonatal erythroderma is typically confused with bullous congenital ichthyosis. The absence of ankyloblepharon can occur in Rapp Hodkgin syndrome, which is now considered part of the AEC spectrum[11].

Evaluation

Diagnosis is first based on the typical phenotypic characteristics of ED, with special emphasis on the presence/absence of sweating, hair/nail, and teeth abnormalities. Further identification of specific syndrome/subtype requires a series of investigations. For example[1-3]:

– Atrichogram will show barcode hair in HED, which will be absent in the hydrotic variant.
– Laboratory work-up with the determination of quantitative immunoglobulin levels and B and T lymphocyte subset populations will be altered in HED associated with primary immunodeficiency.
– Sweat pore counts and pilocarpine iontophoresis may document hypohidrosis and a reduction in the number of eccrine glands.
– Even though usually unnecessary, a skin biopsy shows the absence of eccrine structures in HED or eccrine syringofibroadenomatosis in hydrotic ED.
– Other studies, such as X-rays of the limbs, may aid in diagnosing variants of ED.
– Molecular genetic testing (sequence analysis) allows for disease identification and establishment of risk of transmission.

Treatment/management

As patients with ED are usually children, parent education is of paramount importance, including day-to-day routine management in order to prevent complications. In addition, children and adults with ED must be evaluated individually by multidisciplinary teams, in order to treat multiorgan manifestations.

In general terms, it consists of temperature maintenance and management of congenital defects. For instance, older children should be instructed on physical cooling measures such as frequent drinking of cold liquids and special cooling vests for heat-generating activities. Regular use of moisturizers is useful for xerosis and collodion-like presentation. Treatment of chronic erosive scalp dermatitis (AEC syndrome) can be challenging, and the condition is deemed debilitating and refractory. A stepwise approach must be considered, with bland emollients and prevention of secondary infections. However, classic wound regimens typically fail, and even though topical and systemic antibiotics

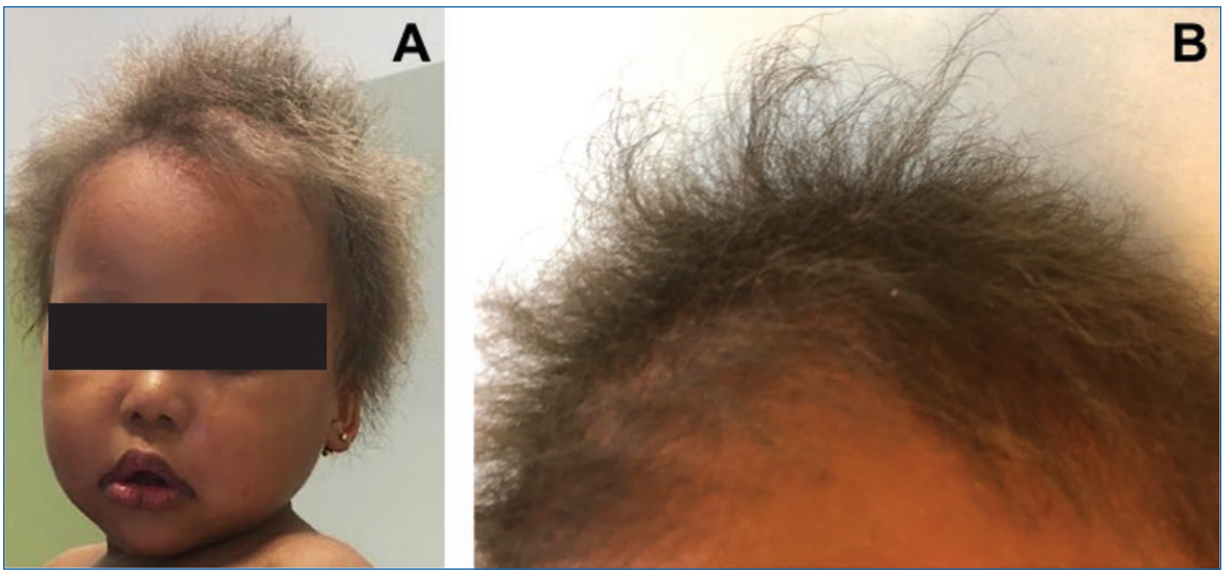

Figure 1. Hypotrichosis with thin rough hair, madarosis, and milphosis.

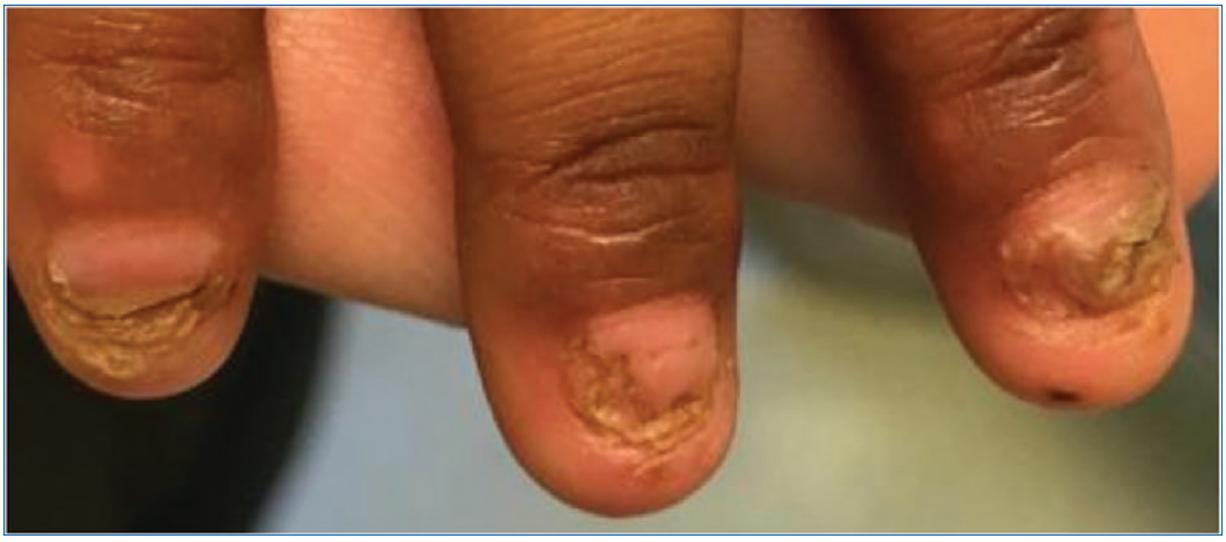

Figure 2. Micronychia.

are often used, they are usually of little benefit except in cases of overt infection[1,2,11]. Improvement with high-potency topical steroids has been advocated in case reports[24], and therefore can be considered in resistant cases.

Early and ongoing dental treatment is essential for the functional and cosmetic outcomes of the teeth. Limb defects, ocular, and other abnormalities require expert reference at the earliest suspicion. Finally, the psychological impact as a consequence of esthetics and abnormal function of orofacial structures should not be overlooked. Referral to the National Foundation of Ectodermal Dysplasias could also prove valuable[1,2,11].

Gene therapy using recombinant gene administration has been evaluated experimentally in animal studies and needs future investigation[25].

Author's experience

A 2-year-old girl presented with alopecia and dystrophic hair and nails. She was otherwise healthy, with an unremarkable familiar history. On examination, there was hypotrichosis with thin rough hair, madarosis and milphosis (Figure 1), micronychia (Figure 2), and heterogeneous skin pigmentation with hyperpigmented areas (Figure 3). There was also apparent hypodontia (Figure 3). A complementary

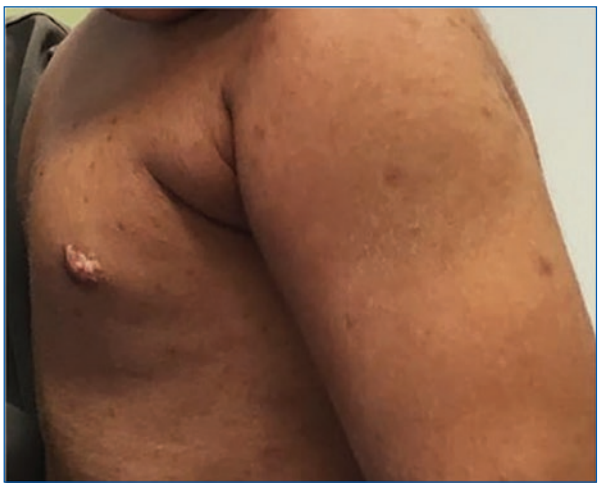

Figure 3. Heterogeneous skin pigmentation with hyperpigmented areas.

investigation revealed a normal blood workup, and primary immunodeficiency was ruled out. An ED was suspected, and genetic testing through next-generation sequencing multigene panel analysis was carried out (Agilent SureSelect Human All Exon® kit and Illumina platform®. Bioinformatics multigene panel analysis comprehending the following genes ATP6V1B2, CDH3, EDA, EDAR, EDARADD, EVC, EVC2, GJB6, HOXC13, IFT122, IFT43, IKBKG, KDF1, KREMEN1, KRT14, KRT74, KRT85, MBTPS2, MSX1, NECTIN1, NECTIN4, NFKBIA, NLRP1, PKP1, SMARCAD1, TP63, TWIST2, WDR19, WDR35, WNT10A). An heterozygous variant c.1963del (p.(Arg655Glufs*49) in exon 14 of TP63 [NM_003722.4] gene was detected. This is a null variant (frameshift), and loss-of-function is a known mechanism of disease in the TP63 gene. This variant is also absent from controls and was previously reported by Rinne et al.[26] in a patient with ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC). These findings are consistent with the AEC syndrome diagnosis, and the patient was managed in accordance, with the pediatrician, odontostomatologist, and dermatologist follow-up.

AEC Syndrome is particularly rare, with about 100 patients reported to date[23]. The most common features, namely skin erosions, orofacial cleft, and ankyloblepharon were missing in our patient, underlining the great interindividual variability. In addition, the latter is missing in Rapp Hodkgin syndrome, regarded as part of the AEC spectrum. These particularities highlight the importance of combined clinical suspicion and genetic analysis.

Concluding remarks

EDs form a diverse group of inherited disorders with variable complications. Molecular findings have helped to elucidate physiopathology and categorize such a heterogenous class, explaining its clinical signs, variability in severity, associated malformations and overlap seen in some ED patients. Equally, such comprehension will lead to future genetically targeted therapeutic approaches. Meanwhile, treatment is symptom-directed, and a multidisciplinary approach is therefore crucial. When achieved, the general prognosis is good with a normal life expectancy, underlining the relevance of an early and careful clinical evaluation.

Ethical responsibilities

Protection of people and animals. The authors declare that for this research no experiments on humans and/or animals were performed.

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

Right to privacy and written consent. The authors declare that they have received written consent from the patients and/or subjects mentioned in the article. The author of the correspondence must be in possession of this document.

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Port J Dermatol and Venereol. **REVIEW ARTICLE**

Where do we stand on adjuvant melanoma therapy?

Qual é a nossa posição sobre a terapia do melanoma adjuvante?

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Abstract

Melanoma remains the deadliest form of skin cancer, and its incidence is increasing. In recent years, melanoma adjuvant therapy has been regarded as a revolution when it comes to prognostic of high-risk melanoma adjuvant therapy has been regarded as a revolution in the prognostic of high-risk melanoma, but questions concerning its indications still challenge the clinical approach. A better understanding of what patients to treat and how to treat them is imperative. Adjuvant therapy is now considered standard of care in many clinical contexts, and currently approved therapies have shown benefit in patients staged III or higher on the American Joint Committee on Cancer (AJCC) 7th edition, which raised issues of adequacy in present clinical settings (AJCC 8th edition). Nevertheless, clinical practice guidelines are unavailable. Furthermore, clinical settings have evolved since the trials that led to the approval of current adjuvant treatments. Completion lymph node dissection is no longer considered standard of care for all sentinel lymph node (SLN)—positive patients, and staging was reconfigured. In light of AJCC's new staging data, early adjuvant therapy –for stage II melanoma– is now under scrutiny. Several breakthroughs are expected in the upcoming years. This review summarizes where we came from, where we are and where we are heading on adjuvant melanoma therapy.

Keywords: Adjuvant. High-risk. Melanoma.

Resumo

O melanoma mantém-se como o mais letal dos cancros de pele e a sua incidência continua a aumentar. Nos últimos anos, o tratamento adjuvante desta patologia contribuiu para uma revolução terapêutica com impacto importante no prognóstico do melanoma de alto risco. Apesar disto, afigura-se como imperativo, ainda, compreender mais detalhadamente quem tratar e quando atuar. A terapêutica adjuvante é atualmente indicada em vários contextos clínicos. As terapêuticas inicialmente aprovadas demonstraram benefício em doentes em estádio III ou superior conforme a 7.ª edição do American Joint Committee on Cancer (AJCC), o que suscitou dúvidas acerca da sua adequação ao atual contexto clínico (8.ª edição do AJCC). Destaca-se, ainda, a reforma à abordagem clínica do melanoma, que evoluiu desde os ensaios que conduziram à aprovação de muitos dos regimes de adjuvância atualmente preconizados. A linfadenectomia total já não é recomendada em todos os doentes com biópsia de gânglio sentinela positiva e o estadiamento foi reconfigurado. Atualmente, à luz da 8.ª edição da AJCC, a terapêutica adjuvante precoce, para os doentes com melanoma em estádio II, é uma realidade sob escrutínio. Esperam-se vários avanços terapêuticos nos próximos anos. Esta revisão pretende explorar de onde viemos, onde nos encontramos e para onde nos dirigimos no que respeita à terapêutica adjuvante no melanoma.

Palavras-chave: Adjuvância. Alto risco. Melanoma.

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Introduction

Melanoma remains one of the most aggressive skin cancers worldwide, and its incidence continues to increase, but a therapeutic revolution has been taking place in the past years[1]. The prognosis is encouraging for early stages, and recent therapeutic options have changed the disease course for more advanced stages with unfavorable prognosis. In fact, low-risk melanomas can be effectively treated with surgery only, but high-risk melanomas with no evidence of disease after excision are associated with worse survival rates[2].

Aiming to offer better therapeutic approaches in the high-risk disease, advances in systemic treatment in the metastatic setting have translated additionally into effective adjuvant therapy for patients with resected but regionally advanced disease[3]. Recently, concerns regarding the choice of optimal adjuvant therapy, evaluation of possible biomarkers, the benefit of adjuvant therapies in stage II patients versus its associated toxicity, as well as the possibility of subsequential treatments over time have been debated.

Where did we come from?

For many years, interferon-α was the only approved option for adjuvant therapy of high-risk melanoma[4]. Since the 1990s, different schedules and protocols were investigated, with a notable effect on relapse-free survival (RFS) but none (or limited effect in specific subgroups) on overall survival (OS)[5]. In fact, despite the apparent benefit from interferon-α in patients with ulcerated primary melanomas[1], the inconsistent improvements shown in OS, along with substantial toxic effects, led to the definite abandonment of this adjuvant therapy, which had never been considered as standard of care in Portugal and worldwide.

Checkpoint inhibitor immunotherapies, including those that target programmed cell death 1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4) and drugs that target the mitogen-activated protein kinase pathway [v-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors and their combination] have recently gained a determinant role in the adjuvant setting[6].

In 2015, ipilimumab, a human antibody against CTLA-4, showed improvement in recurrence-free survival in patients with resected melanoma with involvement of lymph nodes > 1 mm versus placebo. Subsequently, it was shown to improve OS versus placebo (OS at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group) but was associated with serious adverse events leading to early discontinuation in a substantial proportion of patients and death in 1.1%[7]. Nonetheless, this merited approval by the United States Food and Drug Administration, but not the European Medicines Agency (EMA), in the adjuvant setting for melanomas stage III in 2016.

Around 2 years later, nivolumab, a PD-1 checkpoint inhibitor, was approved as adjuvant therapy for melanoma. The CheckMate-238 study compared nivolumab with ipilimumab as adjuvant treatment for patients with high-risk resected stage IIIB-IIIC or resected stage IV melanoma (classified by the AJCC, 7th edition) and has shown the superiority of nivolumab coupled with less toxicity (4-year RFS was 51.7% in the nivolumab group and 41.2% in the ipilimumab group; 4-year OS was 77.9% with nivolumab and 76.6% with ipilimumab; late-emergent grade 3–4 treatment-related adverse events were reported in 1% of patients in the nivolumab group and 2% of patients in the ipilimumab group)[8].

In 2019, another PD-1 inhibitor, pembrolizumab, was approved for melanoma adjuvant treatment as it showed improved RFS versus placebo with no new toxic effects identified (1-year rate of RFS of 75.4% in the pembrolizumab group and 61% in the placebo group)[9].

Regarding targeted therapy, the COMBI-AD study in 2018 established an improvement in RFS when comparing the BRAF inhibitor dabrafenib and MEK inhibitor trametinib to placebo (estimated 3-year rate of RFS was 58% in the combination-therapy group and 39% in the placebo group; 3-year OS rate was 86% in the combination-therapy group and 77% in the placebo group; serious adverse events occurred in 36% of patients in the combination therapy group and in 10% patients in the placebo group)[6]. This data led to the approval of dabrafenib and trametinib as adjuvant treatments for melanoma stage IIIB and higher in 2018.

Where are we?

Adjuvant therapy is changing the way melanoma patients are treated today and is now considered standard of care in most stage III and resected stage IV patients. Both targeted therapy and immune checkpoint inhibitors reduce the risk of recurrent melanoma in high-risk disease[10], as previously discussed. Still, clinical practice guidelines are unavailable, and the decision to prescribe a specific adjuvant therapy requires a detailed selection of patients, evaluating the likelihood of therapeutic efficacy and its associated risks.

Table 1. Comparison between AJCC 7th and 8th edition for stage III subgroups[12]

Stage	AJCC 8th editions			AJCC 7th editions		
	T	N	M	T	N	M
IIIA	T1a/b-T2a	N1a or N2a	M0	T1–4a	N1a or N2a	M0
IIIB	T0	N1b, N1c	M0			
IIIB	T1a/b-T2a	N1b/c or N2b	M0	T1–4b	N1a or N2a	M0
IIIB	T2b/T3a	N1a-N2b	M0	T1–4a	N1b, N2b or N2c	M0
IIIC	T0	N2b, N2c, N3b or N3c	M0			
IIIC	T1a-T3a	N2c or N3a/b/c	M0	T1–4b	N1b, N2b or N2c	M0
IIIC	T3b/T4a	Any N ≥N1	M0	Any T	N3	M0
IIIC	T4b	N1a-N2c	M0			
IIID	T4b	N3a/b/c	M0			

The difficulty of the clinician's approach is highlighted by the absence of measurable disease, making it impossible, contrarily to the metastatic setting, to readily assess a clinical response[11]. As such, a better selection of high-risk of relapse patients could help reduce the costs of toxicity by applying it to the patients that would benefit the most from it. Further research into biomarkers is imperative in this setting.

The 8th edition AJCC melanoma staging system intends to provide a standardized and contemporary cancer staging system that facilitates accurate risk stratification, aiming to guide patient treatment. Well-known clinical-pathological features allowed for this classification: ulceration and Breslow thickness were the most important predictors of survival with respect to the primary tumor (also the extent of vascular invasion in thin melanomas) and, in the N category, the number of the metastatic nodes and whether they present on a clinically occult or clinically apparent fashion and also the presence of in-transit, satellite or locally recurring lesions are of significant prognostic value[12]. Stage III is defined as the presence of nodal, satellite or in-transit metastasis. Most stage III patients are disease-free after surgery, with significantly different relapse risks between subgroups. In AJCC 8th edition, stage III has been further divided into four subgroups allowing for better risk stratification, but there is still room for improvement. Current approval for adjuvant melanoma therapy relied on the 7th AJCC staging system, which raised issues of adequacy in present clinical settings (Table 1). For example, stage III disease in the 7th edition included T1-4a and N1a-2a disease, and the current edition included T1a, T1b and T2a, and N1a-2a status. This is particularly relevant when discussing IIIA or IIIB stages according to the 8th edition because some of these patients would have been classified differently at the time of enrolment in most adjuvant trials[10].

Additionally, other concerns regarding adjuvant trial results validity in today's patient approach have been raised. Since 2015, several adjuvant therapies have been approved based on randomized trials with adjuvant therapy after resection of high-risk disease, and inclusion criteria required performance of a completion lymph node dissection (CLND) after positive sentinel lymph node (SLN) disease. In fact, CLND is no longer considered standard of care for all SLN-positive patients. After the results of the German Dermatologic Cooperative Oncology Group (DeCOG-SLT)[17] and the Multicenter Selective Lymphadenectomy Trial II(MSLT-II)[18], that showed no melanoma-specific survival benefit even if achieving a reduced rate of regional recurrence, some patients are being managed with active nodal surveillance and considered for adjuvant therapy. Some studies have been addressing this issue. Farrow et al. found that adjuvant therapy in patients with a positive SLN who did not undergo CLND has a similar RFS as patients included in adjuvant therapy trials that required CLND[19]. Some authors even believe it is time to reconsider the role of SLN biopsy in melanoma[20]. There is evidently a high need for sensitive and reproducible biomarkers to guide the clinical decision-making process. Efforts have been made to address the issue of better prognostication in melanoma, and additional clinical and histologic features, as well as new biomarkers, have been proposed[11]. Single molecules or specific signatures have been investigated in the monitoring and prognostication of patients: circulating tumor cells are cancer cells circulating in the peripheral blood shed from the primary

tumor or its metastasis, and its utility may land on the real-time detection of subclinical tumor spreading, although lack of standardization remains an issue. Their value relies on the possibility of acting earlier in the case of recurrence[1]. It is also known that melanoma-specific PD-1 overexpression enhances tumor antigenicity. In stage III patients, Madore et al. showed that a PD-L1 negative status related to a worse melanoma-specific survival[13]. Trials with immunotherapy in the adjuvant and advanced setting showed that patients with low immune gene expression had relatively poor clinical outcomes on immunotherapy compared with all other biomarkers subgroups of interest, suggesting a relevant role for immune gene expression status in identifying patients that may derive a clinical benefit from immunotherapy. Dummer et al. recognized the need for the identification of highly predictive clinical and biological characteristics in the attempt to isolate patients with BRAFV600-mutant melanoma who would benefit the most from targeted therapy or checkpoint inhibitor therapy in adjuvant and metastatic settings. Their results showed that a high interferon-γ gene expression signature was prognostic for prolonged RFS in both dabrafenib plus trametinib and placebo groups. Tumor mutational burden (TMB) provided prognostic value in the placebo group but not the dabrafenib plus trametinib group, with a low TMB associating with a greater benefit from treatment with dabrafenib plus trametinib and a high TMB correlating with less benefit from dabrafenib plus trametinib treatment, particularly if there was a low interferon-γ signature[14]. On the other hand, high TMB was associated with improved RFS with adjuvant nivolumab therapy. However, the efficacy of PD-1 blockade in this setting with concomitant low interferon-γ gene expression signature or other negative immune biomarkers is unclear[15]. This discussion seems particularly important when realizing that, ultimately, in the treatment groups of several published trials on adjuvant therapy, many patients still relapsed (42% for dabrafenib plus trametinib[6], nearly 30% for nivolumab[16] and approximately 25% for pembrolizumab[9]). A better understanding of what patients to treat and how to treat them is imperative.

Where are we heading?

Early adjuvant therapy is under scrutiny. The discussion centers itself around the potential positive impact on overall deaths from melanoma as we begin to treat more patients with early-stage disease, given the large number of patients diagnosed in this stage and its unnecessary prospective toxicity costs.

It is known that patients with stage IIC disease have a worse prognosis than those with stage IIIA disease. Also, patients with stage IIA or IIIA disease have a similar melanoma-specific survival - of 94% or 93%, respectively at 5 years[10]. Estimates of the number of patients with stages IIB and IIC melanomas that remain at high-risk of relapse and may benefit from adjuvant therapy are significant. Approximately one-half of patients with stage II melanoma will have stage IIB or IIC disease and are at the highest risk of recurrence, which roughly parallels the number of stage III melanoma patients, for which adjuvant therapy is standard of care[21]. In stage II patients, rates of distant recurrence after resection can reach 44%[22].

On the other hand, consideration of the potential permanent adjuvant treatment toxicity may imbalance the risk/benefit appreciation as we consider the treatment of patients with earlier-stage disease, many of whom may already have been cured by surgery[21].

Unlike interferon-alfa, associated with substantial adverse events and fatalities, modern adjuvant therapies are expected to have a more favorable safety profile. To date, monotherapy with pembrolizumab or nivolumab has been shown to have a considerably better tolerability profile than ipilimumab, and the dabrafenib plus trametinib combination demonstrated similar grades of adverse events rates as pembrolizumab and nivolumab. Combination immunotherapy with ipilimumab/nivolumab and ipilimumab monotherapy was associated with the highest toxicity.

Considering the curative setting where adjuvant treatment plays a role, potentially permanent toxicities involved with immune checkpoint inhibitors became particularly relevant, especially hypophysitis, hypothyroidism, primary adrenal insufficiency, and insulin-dependent diabetes[2]. In fact, chronic adverse events associated with anti-PD-1 therapy appear to be more common than previously recognized and frequently persist even with prolonged follow-up. Although most are low-grade, the risk of triggering chronic adverse events should be integrated into treatment decision-making[23].

Another limitation of a protocoled approach to these patients is the lack of comparative analysis between different treatment options. Although there is a phase III trial comparing ipilimumab and nivolumab versus dabrafenib plus trametinib in stage III-IV unresectable BRAFV600 positive melanoma, there are no results from a head-to-head comparison of immune checkpoint

inhibition versus targeted therapy, leaving the decision-making to be guided by individual patient and tumor characteristics in BRAFV600 positive patients[10]. Review using Bayesian network meta-analysis investigated RFS, distant metastasis-free survival and OS in adjuvant trials that tested dabrafenib plus trametinib, nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy, and interferon-α. The study concluded that efficacy was comparable between targeted therapy (dabrafenib plus trametinib) and anti-PD-1 inhibitors[24]. However, the optimal sequencing of therapy options in BRAF-mutated patients remains to be determined[25].

Although interferon-α remains an adjuvant alternative for patients with stages IIB and IIC, it is rarely used due to its toxicity[4,26]. Given the clinical benefit observed with adjuvant pembrolizumab in patients with stage III melanoma, a strong rationale exists to determine if a similar benefit could be attained in adult and pediatric patients with high-risk resected stage II disease. KEYNOTE-716 is a randomized, double-blind, phase 3 trial that compared pembrolizumab to placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma. Its results have been recently published (March 2022) and demonstrate that pembrolizumab, as adjuvant therapy for up to approximately 1 year for stage IIB or IIC melanoma, resulted in a significant reduction in the risk of disease recurrence or death versus placebo, with a manageable safety profile[22]. These initial conclusions will change the way we treat high-risk melanoma patients. As previously discussed, stage IIB and IIC RFS parallels with the RFS for stages IIIA and IIIB. Following this rationale, it is expected that adjuvant therapy could be used, with favorable results, in these, not previously considered, high-risk patients. In December 2021, the Food and Drug Administration approved pembrolizumab for adjuvant treatment of stage IIB or IIC melanoma patients based on KEYNOTE-716 results. Recently, the EMA also approved pembrolizumab for adjuvant treatment of completely resected stage IIB and IIC melanoma patients. Naturally, more mature data regarding follow-up and survival will only be available in the upcoming years.

Another phase II trial is currently studying how well nivolumab works in treating patients with stage IIB-IIC melanoma that can be removed by surgery and is expected to be completed in 2023 (ClinicalTrials.gov Identifier: NCT03405155).

Melanoma adjuvant therapy will most certainly not be limited to the previously discussed treatments. Desmoplastic neurotropic melanomas show higher rates of local recurrence after wide local excision, and data suggests that adjuvant radiation in this setting can be helpful. ANZMTG 01.02/TROG 02.01 trial looked at the utility of adjuvant nodal radiotherapy after lymphadenectomy. After a median follow-up of 73 months, nodal relapse occurred in 21% of the adjuvant radiotherapy group compared with 36% in the observation group, but there was no difference in OS or RFS[27]. Agrawal et al. stated that radiotherapy was significantly associated with a lower risk of regional recurrence[28]. Although these data suggest a potential benefit to adjuvant radiotherapy in well-selected patients, most data are from before the era of immunotherapy[29].

Vaccines have also been trying to take their place in adjuvant therapy, such as whole cells (cell lysates), peptide vaccines, and ganglioside antigen vaccines, but have generally failed to demonstrate significant benefits[24].

Neoadjuvancy, beyond the scope of this review, has also been recently discussed, with promising results. The OpACIN-neo phase II trial was designed to identify an effective and safe dosing schedule for the combination of neoadjuvant ipilimumab and nivolumab in stage III melanoma. PRADO, an extension cohort of this trial, aims to confirm the pathologic response rate and safety of neoadjuvant ipilimumab 1 mg/kg and nivolumab 3 mg/kg to assess response-driven subsequent therapy in stage III melanoma. Its recent results seem to show that patients with resectable stage III melanoma who have a major pathologic response to neoadjuvant therapy can skip therapeutic lymph node dissection and adjuvant therapy, which is associated with morbidity and still achieve high 2-year rates of RFS[30].

Adjuvant treatment in melanoma has come a long way since its early years. New treatments have changed the management of the disease, and more breakthroughs are to be expected in the next few years. Not only the discovery of novel or reinvented drugs is anticipated but also a better understanding of what patients to treat, how to do it and when to act, all to the benefit of melanoma patients.

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.

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CASE REPORT

Erythroderma as first sign of lung cancer

Eritrodermia como primeira manifestação de carcinoma do pulmão

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Abstract

Erythroderma, or generalized exfoliative dermatitis, is a rare inflammatory disorder characterized by generalized erythema, involving more than 90% of the body surface area, accompanied by a variable degree of scaling. It may be the clinical presentation of several cutaneous or systemic diseases and it is frequently challenging to find the underlying cause. Our case focuses on a 76-year-old male patient that was referred to our department due to generalized erythroderma and diffuse alopecia, developing over the last 4 months. He presented with erythematous papules and nodules, some of them covered with sticky scales. Skin biopsy was compatible with drug eruption. Due to an inadequate response to treatment and typical B symptoms, further imagiologic studies were performed. Ultimately he was diagnosed with non-small cell lung cancer. This case shows the need to search for a neoplasm in patients presenting with erythroderma, particularly in the presence of systemic symptoms.

***Keywords*:** Erythroderma. Paraneoplastic dermatitis. Lung cancer.

Resumo

A eritrodermia pode ser a apresentação clínica de doenças cutâneas ou sistémicas severas, e caracteriza-se por eritema envolvendo mais de 90% da superfície corporal, acompanhada de variados graus de descamação. Encontrar a causa subjacente é frequentemente desafiador. Descreve-se o caso de um doente do sexo masculino de 76 anos, observado na consulta de Dermatologia por eritrodermia e alopécia difusa, com 4 meses de evolução. Ao exame físico observava-se uma dermatose polimórfica constituída por eritema e descamação generalizados, associados a pápulas e nódulos eritematosos e queratodermia palmar. A biópsia cutânea foi compatível com toxidermia. Por ter apresentado má resposta à terapêutica instituída e apresentar sintomas B típicos, foram realizados estudos imagiológicos. O diagnóstico final foi de carcinoma do pulmão de não-pequenas células. Este caso demonstra a necessidade de procurar uma neoplasia num doente que se apresente com eritrodermia, principalmente na presença de outros sintomas sistémicos e sem dermatose prévia.

***Palavras-chave*:** Eritrodermia. Dermatose paraneoplásica. Neoplasia do pulmão.

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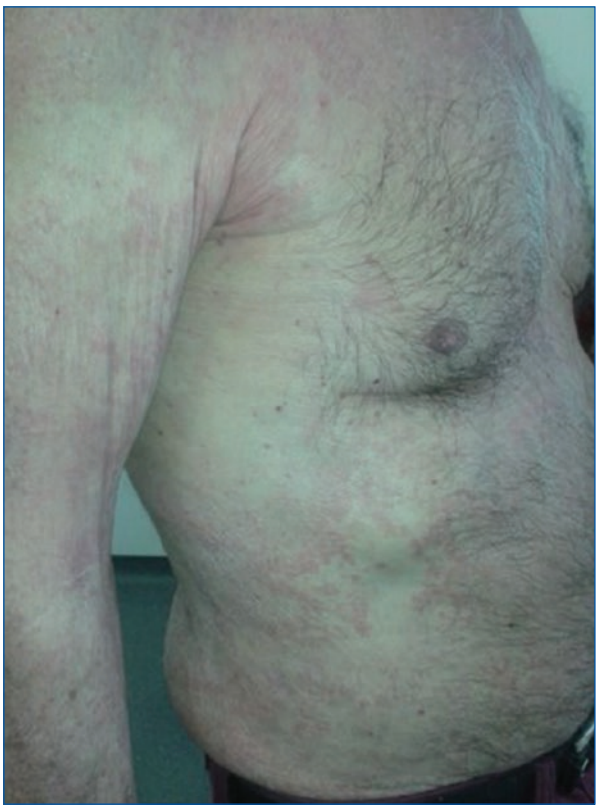

Figure 1. Generalized erythrodermic rash on the trunk and upper limbs.

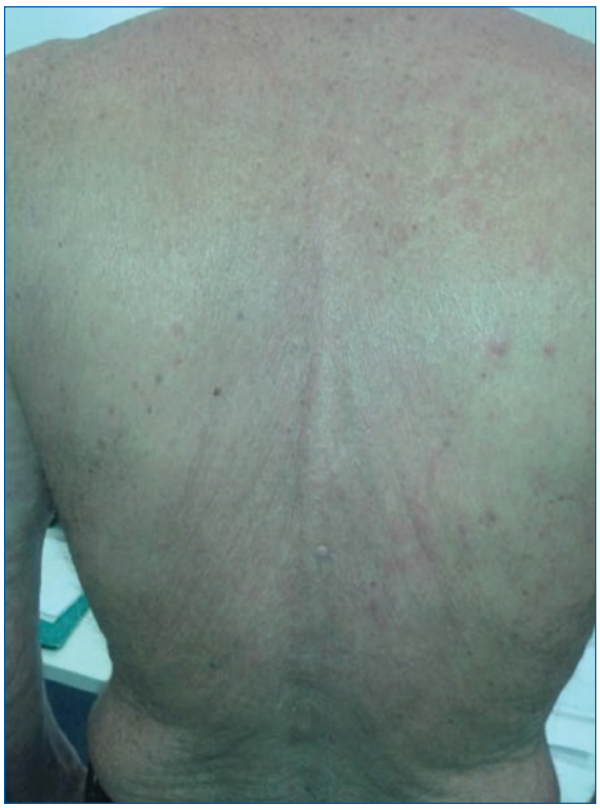

Figure 2. Generalized erythrodermic rash on the trunk and upper limbs.

Introduction

Erythroderma, or generalized exfoliative dermatitis, is a rare inflammatory disorder characterized by generalized erythema, involving more than 90% of the body surface area accompanied by a variable degree of scaling.

Establishing the underlying diagnosis may be very difficult initially. Erythroderma may be the clinical presentation of several cutaneous or systemic diseases. However, it is a rare first manifestation of a solid organ malignancy[1,2].

Our case report describes one of the rare dermatological presentations of lung cancer.

Clinical case

A 76-year-old male patient presented to the dermatology appointment with generalized erythroderma and diffuse alopecia.

As personal priors, he had hypertension and type 2 diabetes *mellitus*, treated with acetylsalicylic acid, atorvastatin, amiloride, and metformin. He offered no previous history of eczema, psoriasis, or any other skin conditions.

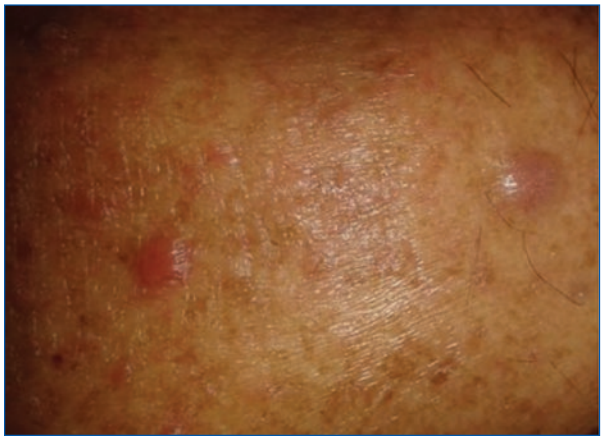

Figure 3. Associated erythematous papules and nodules, some of them covered with sticky scales, widely distributed throughout the entire body.

The skin rash appeared 4 months ago and he was evaluated in a private dermatology practice, where blood tests and a skin biopsy were performed. The routine laboratory showed peripheral eosinophilia and the histopathological findings were compatible with drug eruption.

Since there was a suspicion of toxicoderma, all of the patient's chronic medication was suspended. A

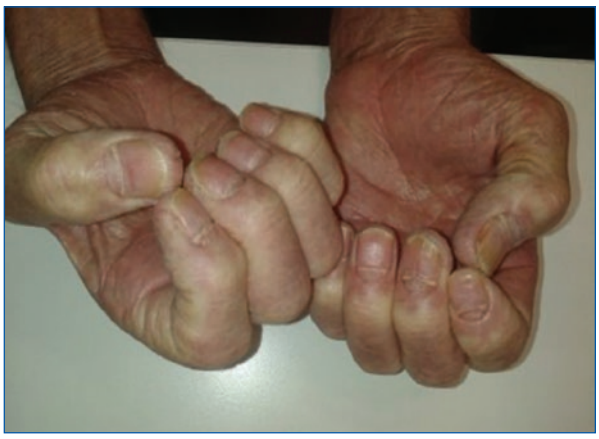

Figure 4. Palmar and ungueal involvement.

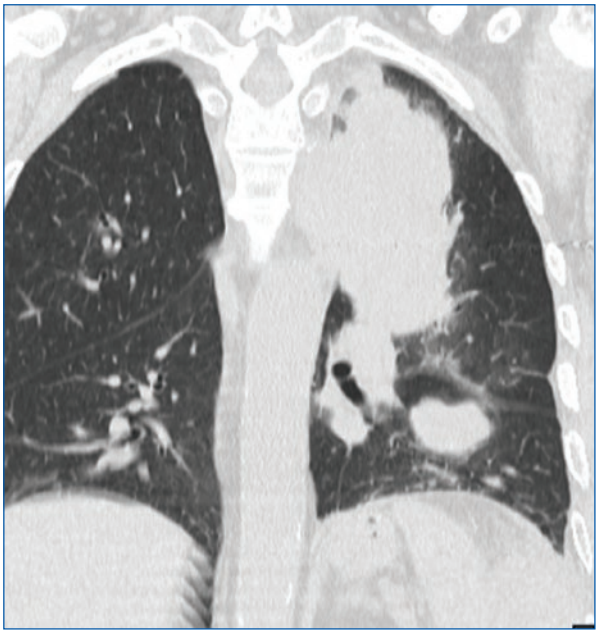

Figure 5. Chest CT scan showed multiple nodular lesions on the left lung, the biggest with 10 cm in diameter.

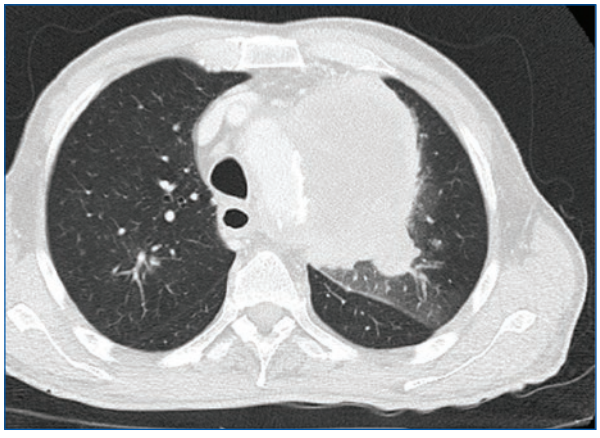

Figure 6. Chest CT scan showed multiple nodular lesions on the left lung, the biggest with 10 cm in diameter.

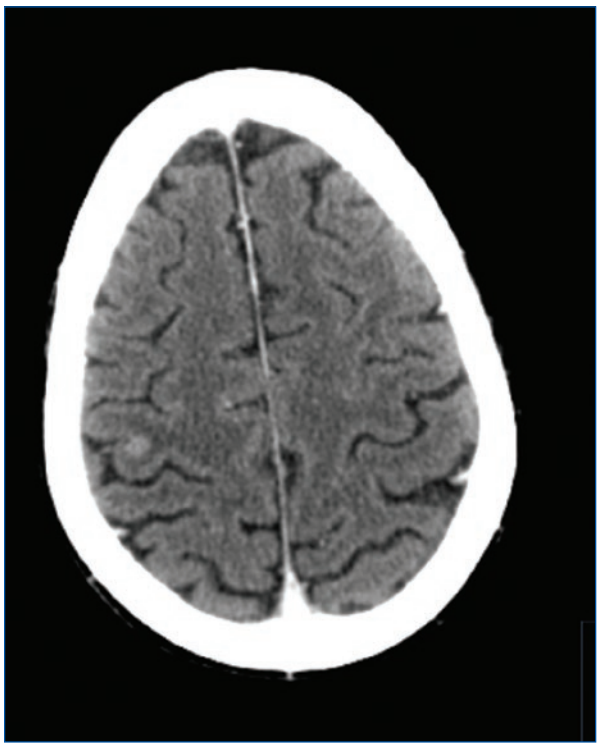

Figure 7. Head CT scan and positron emission tomography demonstrated metastatic lesions in the central nervous system, colon, muscle and bone.

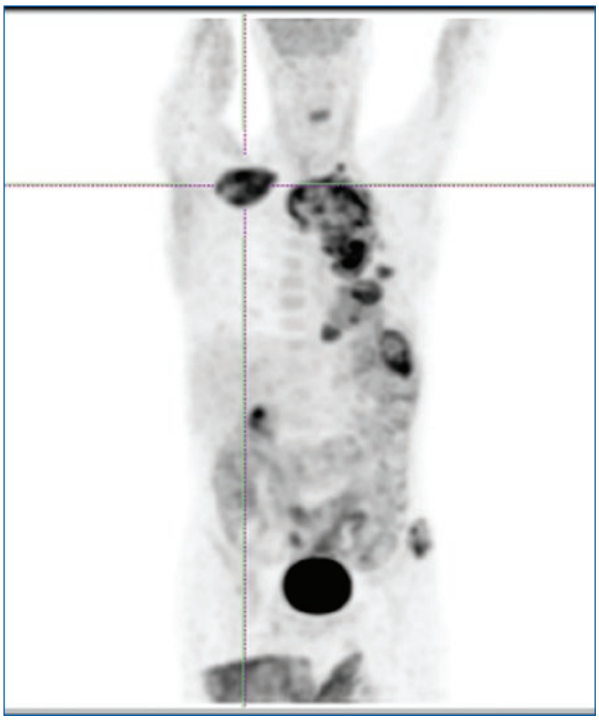

Figure 8. Positron emission tomography demonstrated metastatic lesions in the colon, muscle and bone.

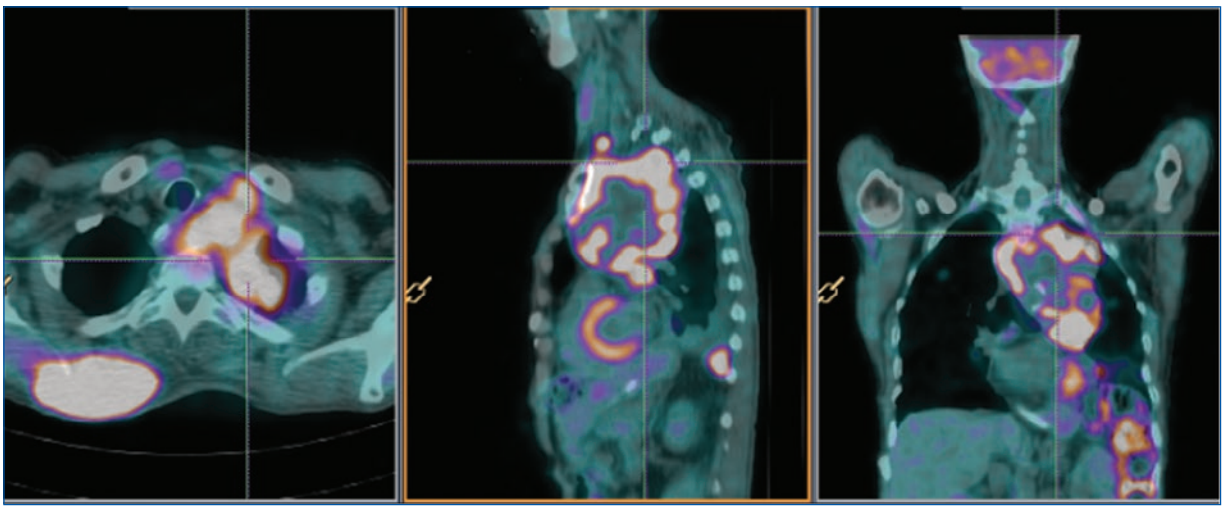

Figure 9. Positron emission tomography demonstrated metastatic lesions in the colon, muscle and bone.

variety of treatments were attempted throughout the months, including cyclosporine, corticotherapy (topical, per os, and intramuscular), and azathioprine, but the patient showed no improvement at all.

At this point, the patient presented to our dermatology department. Dermatological examination revealed a polymorphous dermatosis, with a generalized erythrodermic rash on the trunk, upper and lower limbs, face, and dorsum of hands and feet, associated with sparse erythematous papules and nodules, some of them covered with sticky scales, widely distributed throughout the entire body (Figures 1–3). Additionally, the patient presented with onychomadesis and subungual hyperkeratosis of the fingernails, and palmoplantar keratoderma (Figure 4).

A new skin biopsy was performed and the histopathological findings matched the previous diagnosis of allergic eczema/drug eruption, with tissue eosinophilia.

The patient was treated with topical corticotherapy and hydroxyzine.

Two months later, with no improvement of the skin rash, he started with complaints of partial dysphonia, anorexia, weight loss (10 kilos in 5 months), and a fast decline in overall health status.

Full laboratory blood tests showed an elevated alkaline phosphatase and sedimentation rate. Chest radiography revealed a mass on the upper left thorax. Further study with computed tomography (CT)—scan showed multiple nodular lesions on the left lung, the biggest with 10 cm in diameter (Figures 5 and 6). The histopathology was compatible with squamous cell lung cancer. Head CT and positron emission tomography demonstrated metastatic lesions in the central nervous system, colon, muscle, and bone (Figures 7–9). Unfortunately, the patient passed away a few months later.

Discussion

Erythroderma is a severe inflammatory skin syndrome characterized by generalized erythema and desquamation comprising ≥ 90% of the body surface area. It is most commonly caused by atopic dermatitis, psoriasis, and drug reactions. In some cases it is idiopathic, and these patients should be closely monitored over a long period of time, with skin biopsies, since some of these will develop a cutaneous T-cell lymphoma[3].

Paraneoplastic erythroderma accounts for about 1% of the cases and is most commonly associated with lymphoproliferative disorders, other than mycosis fungoides and Sézary syndrome. Less commonly, it can be associated with solid tumors, usually in the late stage of the disease, including colon, prostate, gastric, and lung carcinoma[4-6]. Paraneoplastic syndromes can appear before, during or after the tumor diagnosis[1]. In this case it was the first manifestation.

Lung cancers are a leading global cause of morbidity and mortality[7]. The most common paraneoplastic dermatoses associated with lung neoplasms are tripe palms, erythema gyratum repens, hypertrichosis lanuginosa acquisita, and Bazex syndrome[8].

To our knowledge, as an erythroderma presentation, only 14 cases of squamous cell lung cancer have been reported in the literature[7,9]. Following Curth's postulates, we can relate but not definitely classify this case

of erythroderma as a paraneoplastic syndrome, since the patient wasn't able to initiate treatment[9].

A limitation of this study is the fact that the skin nodules weren't biopsied, which might mean apart from erythroderma, the possibility of a cutaneous metastasis from lung cancer.

A clinical finding of a rapidly extending erythroderma, especially in a patient without any previous dermatological disorder and with systemic symptoms, should warrant investigation for underlying malignancies.

Recognition of these paraneoplastic dermatoses is important to facilitate earlier diagnosis and management.

Ethical responsibilities

Protection of people and animals. The authors declare that for this research no experiments on humans and/or animals were performed.

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

Right to privacy and written consent. The authors declare that they have received written consent from the patients and/or subjects mentioned in the article. The author of correspondence must be in possession of this document.

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CASE REPORT

Can't you see? It's a Cupid's bow basal cell carcinoma!

Dificil de ver: é um basalioma do arco de cupido

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Abstract

Epithelial tumors, and in particular basal cell carcinoma (BCC), extremely rarely affect the area known as Cupid's bow, and their treatment remains a serious challenge. We present a 53-year-old patient with a history of painful sunburns in the past and BCC of the neck, successfully treated surgically. The reason for the hospitalization was the appearance of a new nodular achromic lesion in the area of ″Cupid's bow″ (upper lip), which preoperatively was verified histopathologically as BCC. Elliptical excision under local anesthesia was performed, and the resulting defect was closed using an undermining surgical approach, followed by single skin sutures. The patient's 4-month follow-up was uneventful with no evidence of recurrence. Treatment options for BCCs in the area of Cupid's bow and the advantages of elliptical excision in the area are discussed.

***Keywords*:** BCC. Cupid's bow. Dermatologic surgery. Undermining surgical approach. Erogenous zone. Elliptical excision.

Resumo

Os tumores epiteliais, e em particular o BCC, afectam muito raramente a área conhecida como arco de Cupido, e o seu tratamento permanece um sério desafio. Apresentamos um paciente de 53 anos com um histórico de queimaduras solares dolorosas no passado e carcinomas basocelulares (BCC) do pescoço, tratado cirurgicamente com sucesso. O motivo da hospitalização foi o aparecimento de um novo nodular lesão acrómica na área de ″Cupid's bow″ (lábio superior), a qual foi verificada histopatologicamente, antes da operação, como BCC. Elíptica excisão sob anestesia local foi realizada, e o defeito resultante foi fechado usando uma abordagem cirúrgica minadora, seguido de suturas de pele simples. O seguimento de 4 meses do paciente foi sem problemas, sem evidências de recidiva. Tratamento são discutidas as opções de BCC na área do arco do Cupido e as vantagens da excisão elíptica na área. Palavras-chave: BCC. Arco de Cupido. Cirurgia dermatológica. Abordagem cirúrgica de submineração. Zona erogénica. Excisão elíptica.

Introduction

In practice, the lips are an important organ and have a key role both in food intake, the formation/articulation of speech, and the sounds, we produce[1-3]. On the other hand, the lips are also a tactile-sensory organ, an erogenous zone of particular importance in relation to the concept of intimacy[2,3]. Precisely because of this, the preservation of their integrity (of the lips) is largely related to the preservation of the concepts such as individuality, uniqueness, and identity.

The damage to their shape or ″external frame″ could have a serious impact on the psycho-emotional state of the patients even when the esthetic side of this

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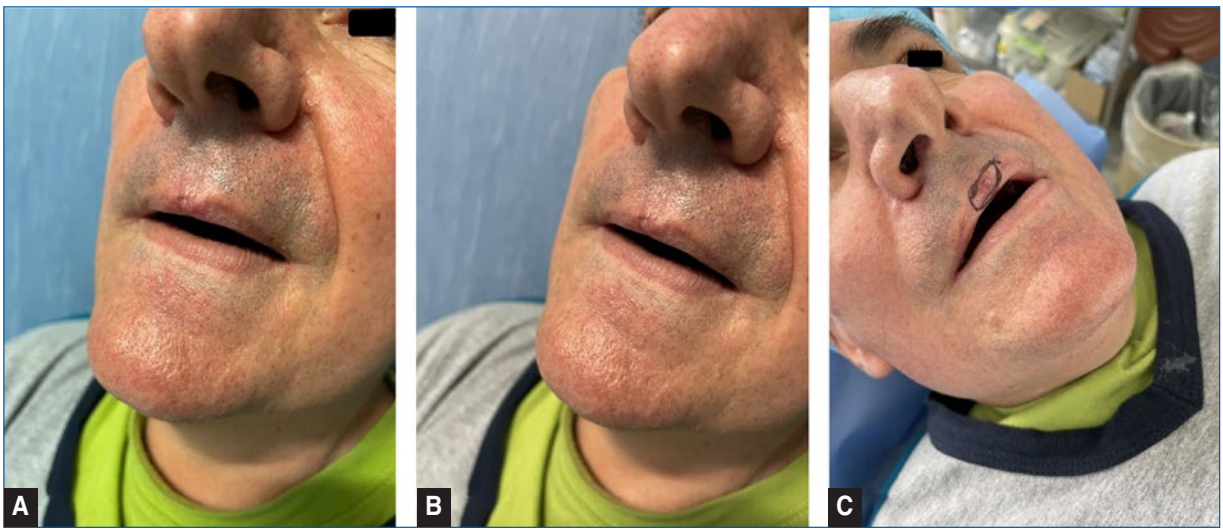

Figure 1. A and **B**: achromic tumorous formation in the area of the upper lip or the so-called Cupid's bow. **C**: preoperative marking of the resection lines before anesthetic administration.

problem is completely resolved in their favor and facial disproportions are absent to minimal[4]. Any change in this area remains ″painful″ for patients regardless of age and the achieved postoperative results[4].

From a practical point of view, a mandatory step in determining the surgical or therapeutic plan should be performing a skin/mucosal biopsy, which is needed for the various future therapeutic options, possible radiation therapy, local application of imiquimod, determination of recommended or ″reduced″ resection margins fields (performed for a better cosmetic result), prepared for adaptation to the compromised motility of the lips in the postoperative period, the necessity of disease staging, the patient follow-up during certain periods, etc.[5]. Informed consent is mandatory and should be discussed carefully and in detail.

Case report

A 53-year-old male reported to the dermatology department with primary complaints of an elevated achromic tumorous formation on the upper lip in the area of the Cupid's bow over the past 6 months (Figures 1A and 1B), which started bleeding and growing in the previous 2 months. A biopsy confirmed basal cell carcinoma (BCC). The patient denied having allergies or any form of skin cancer in any family member. The previous history of two BCC's in the neck area was reported. Concomitant diseases: hypercholesterolemia, hypertriglyceridemia.

The patient with a phototype II was otherwise healthy, orientated, and in good condition. The laboratory results showed normal values for the total serum protein- 94.0 gm/L (norm 64-83), triglycerides- 2.76 mmol/L (norm 0.2-1.7), cholesterol- 8.04 mmol/L, LDL- 5.6 mmol/L (norm 1.5-3.0). An ECG showed sinus rhythm with a left anterior hemiblock, thorax X-ray was normal, ultrasound of the neck showed no pathologic lymph nodes, and Doppler revealed 50% stenosis of the right internal carotid artery.

The patient underwent surgical excision with 0.35 mm margins in all directions (Figures 1C, 2A and 2B).

The lesion has been removed by elliptical excision without resectioning the muscles in the depth. In order to close the defect adequately, the tissue has been mobilized and closed by single interrupted sutures.

Histopathology showed an adenoid cystic variant of BCC measuring 2/4 mm with clean resection lines.

A severe swelling of the upper lip was observed postoperatively (Figure 2B). The patient received methylprednisolone 20 mg i.v., once daily for 5 days, and desloratadine 5 mg once daily for 6 days, combined with daily dressings with povidone-iodine 10% ointment, with visible improvement of the upper lip edema.

Discussion

BCC is one of the most common types of skin cancer in photo exposed areas[6]. It should be noted that the labial mucosa is not the characteristically nor the typical area within which BCC manifests clinically[7,8]. About 90% of skin tumors affecting the lips are squamous/keratinocytic carcinomas[9]. Although extremely rare, when present, BCCs primarily affect the upper lip[4].

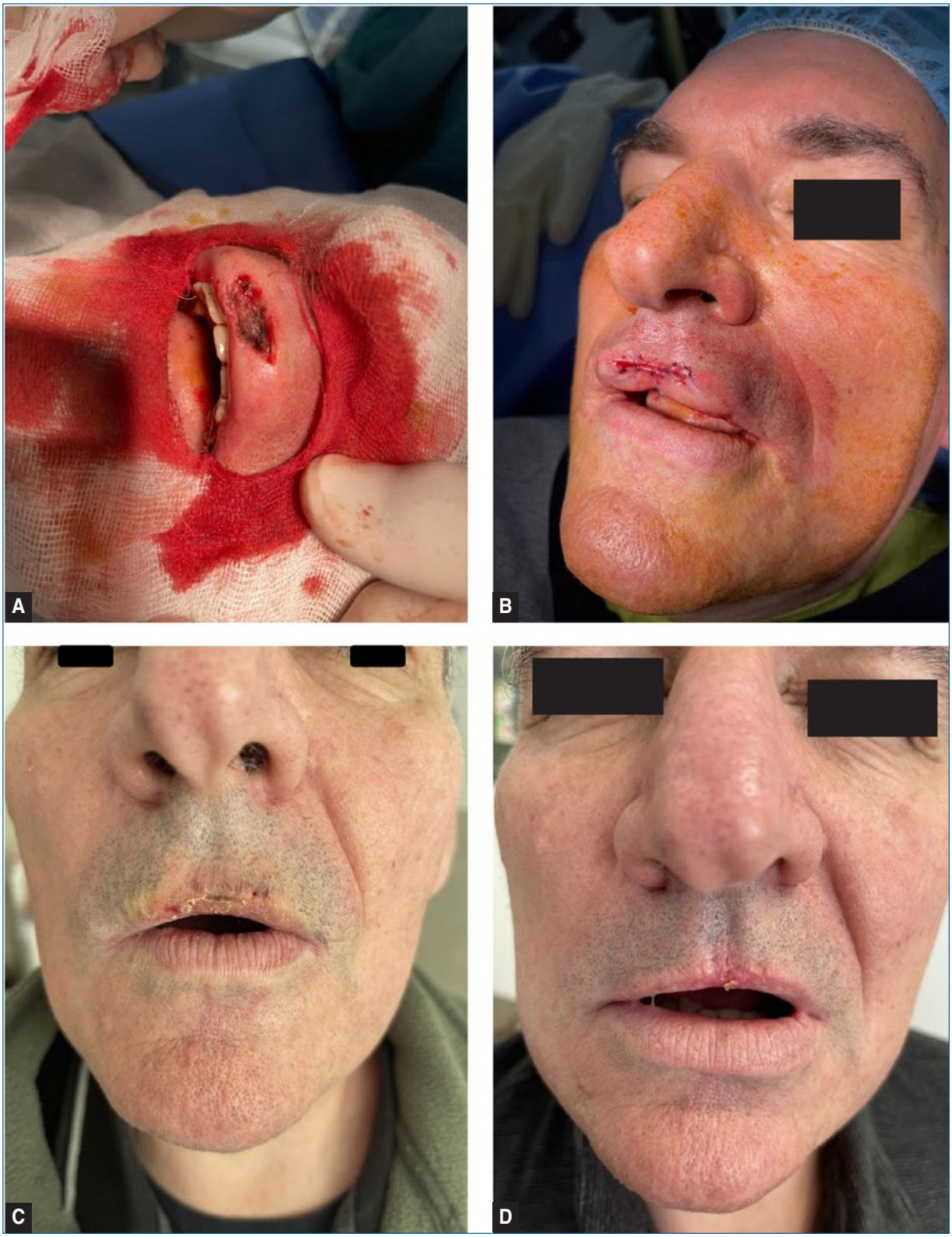

Figure 2. **A**: intraoperative finding after removing the tumor formation and stopping the bleeding with electrocautery. **B**: intraoperative finding immediately after closure of the defect with single skin sutures. **C**: postoperative finding on day 10. **D**: clinical status after 4 weeks.

According to other authors' collectives, the incidence of BCCs in women in this area prevails significantly[9].

The main pathogenetic mechanisms for the induction of this type of neoplasms are associated with prolonged exposure to sunlight, geographic location, race, immune status, as well as some genetic features[10,11].

The pathogenetic hypotheses regarding the development of basal cell carcinomas in the area of the upper lip are interesting and largely divergent, as (1) they include the transformation of the pluripotent epithelial cell of the oral mucosa and epidermis to a tumor cell, while (2) other authors believe that the transformation to a malignant branch starts from the ectopic sebaceous glands[9].

Regardless of these mechanisms, early treatment of BCCs of the upper lip is and should remain a priority due to the propensity of tumor complexes for rapid deep invasion[7].

The uniqueness of the finding shared by us- BCC in the area of the upper lip, is confirmed by a number of extensive literature observations[12-14].

Back in 1949, a study of 620 cases of BCCs of different/variable localization, found only two cases of BCCs of the lower lip[12].

A similar study of 625 cases of BCCs from 1975, again found a limited number of BCCs of the lips: three cases of BCC of the vermilion mucosa[13].

In 1998, another scientific work focused attention on three new cases of BCC of the vermilion zone, but again on the lower lip, treated surgically by Mohs surgery[14].

Reconstruction after removal of epithelial tumors in the area of ˝Cupid's bow˝ remains a serious clinical/dermatosurgical challenge, as it requires the precise application of a number/of different plastics such as Mohs micrographic surgery, followed by a flap or a skin graft or mucosal advancement flap[15], simultaneously used of two vermilion flaps and a rotational skin flap[16].

The data in the medical literature, on the application of elliptical excision in the Cupid's bow area, followed by undermining approach and defect closure with single interrupted stitches or the surgical solution proposed and carried out by our team (Figures 1 and 2), is limited. It requires massive infiltration of the tumor area with lidocaine 2% and adrenaline diluted with saline, thus inducing flattening of the physiological folds in and around the tumor area, the so-called Cupid's bow area. This smoothens the compliance with the resection lines and adaptation of the wound edges subsequently (Figure 2B).

If edema persists, the systemic administration of corticosteroids and antihistamines are also possible, similar to the patient's description. This guarantees a gradual ˝shrinkage of edema˝ in the postoperative period, as well as the parallel occupation of the selected position of the physiological folds in the area of Cupid's bow (Figures 2C and 2D).

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.

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CASE REPORT

Chronic lichenoid keratosis with good response to oral acitretin: a case report

Queratose liquenoide crônica com boa resposta a acitretina oral: relato de um caso

Mariana S. Bernardes[1], Jéssica C. N. Araújo[1], Luísa L. Macias[1], Laísa E. De Hollanda[1], Joelly T. L. Levermann[1], Alcidarta R. Gadelha[2], Patricia C. B. De Melo[1], and Luciana M. Dos Santos[1]*

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Abstract

Keratosis lichenoides chronica or Nekam's disease is a rare disease of unknown etiology and pathogenesis, with few cases described in the literature. The lichenoid-like lesions as well as their histopathological findings require a wide range of differential diagnoses. Its chronic, progressive course and refractoriness to topical and systemic therapies are hallmarks of this dermatosis. The aim of this report is to describe the case of a patient with typical cutaneous manifestations and compatible histopathological findings with a good response to acitretin.

***Keywords*:** Keratosis. Lichenoid eruptions. Skin diseases. Retinoids.

Resumo

A queratose liquenóide crônica ou doença de Nekam é uma doença rara, de etiologia e patogênese desconhecida, com poucos casos descritos na literatura. As lesões de aspecto liquenóide assim como seus achados histopatológicos requerem um amplo leque de diagnósticos diferenciais. O seu curso crônico, progressivo e a refratariedade às terapias tópicas e sistêmicas são características marcantes dessa dermatose. O objetivo deste relato é descrever o caso de um paciente com manifestações cutâneas típicas e achados histopatológicos compatíveis com boa resposta à acitretina.

***Palavras-chave*:** Queratoses. Erupções liquenoides. Dermatopatias. Retinoides.

Introduction

Keratosis lichenoides chronica (KLC) or Nekam's disease is a rare disease of unknown etiology, a chronic course, and progressive character, with less than 150 cases published to date. Clinically, it presents with lichenoid papules arranged linearly or in a reticulated pattern on the extremities and trunk, together with facial erythema in a seborrheic distribution, oral erosions, nail, and genital involvement[1,2]. Due to the rarity of the cases and unknown pathophysiology, it becomes a therapeutic challenge.

The aim of this report is to describe the case of a patient with typical cutaneous manifestations and compatible histopathological findings, with a good response to acitretin.

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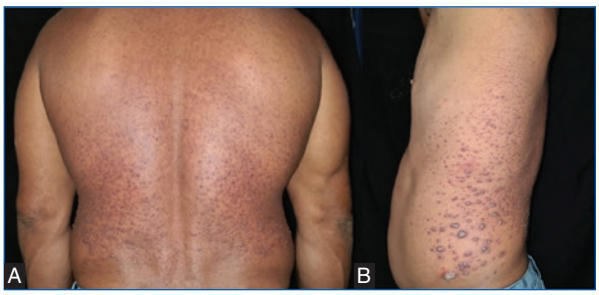

Figure 1. A: violaceous hyperkeratotic papules forming plaques on the dorsum. **B:** linear distribution of lesions with the confluence of some generating a reticulated appearance.

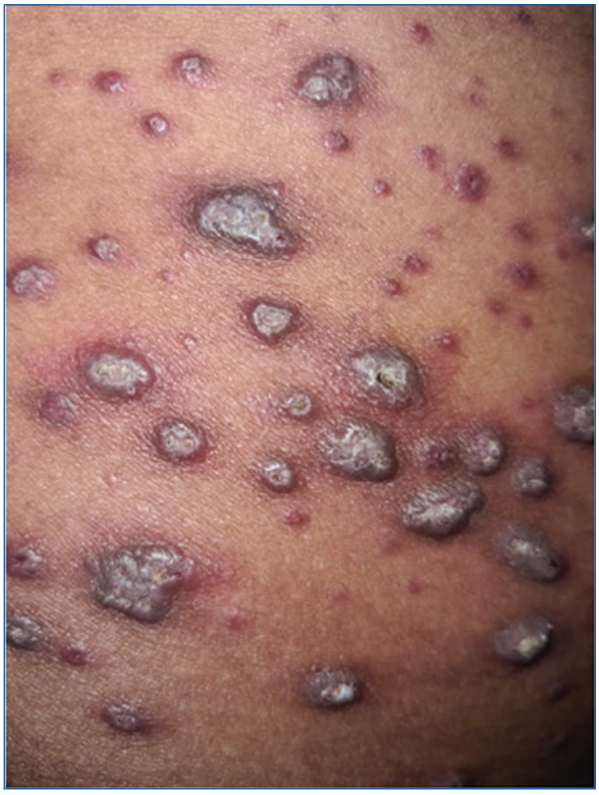

Figure 2. Detail of violaceous, confluent, hyperkeratotic papules in a linear and reticulated pattern.

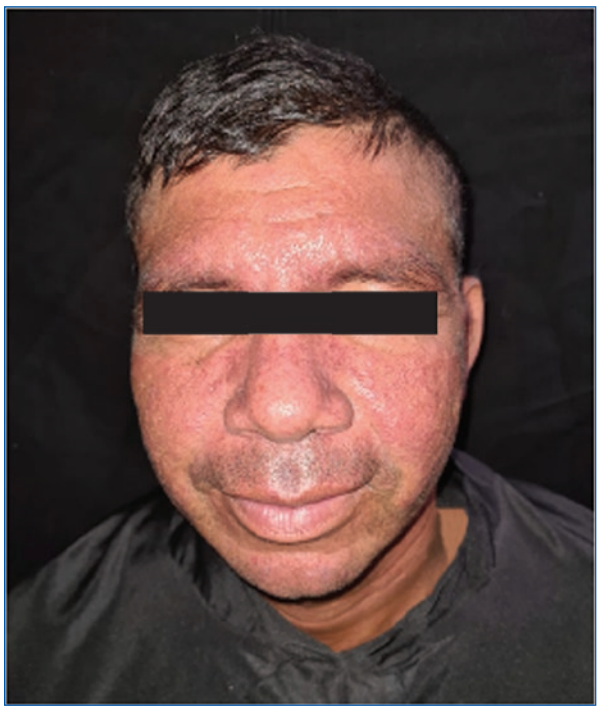

Figure 3. Diffusely infiltrated facial lesions with diffuse erythema and telangiectasia affecting predominantly convex areas.

Case report

A 42-year-old male patient, born and living in the municipality of Tefé, in the interior of Amazonas State (Brazil), complained for approximately 12 years of hyperkeratotic, pruritic, erythematous papules and plaques, some arranged in a parallel linear pattern and others in a reticular shape, symmetrically distributed on the back (Figures 1 and 2). Dermatological examination also showed erythema, edema, and facial telangiectasia with a rosacea-like appearance (Figure 3). Laboratory tests, including blood count, liver and kidney function, rheumatologic markers, serologies for human immunodeficiency virus (HIV), syphilis, hepatitis B and C, and urinalysis, were unaltered. An incisional biopsy was performed, and the anatomopathological examination revealed a hyperkeratotic epidermis, with foci of parakeratosis, large ortho- and parakeratotic corneal plugs, moderate irregular acanthosis, marked vacuolar degeneration of the basal layer, and rare individually necrotic keratinocytes (Figure 4). In the dermis, there were numerous lumps of melanin, free and within macrophages, and moderate perivascular, perifollicular, and interstitial infiltrate composed of lymphocytes, histiocytes, melanophages, and macrophages (Figure 5). Within the differential diagnoses of a lichenoid eruption, lichen planus (LP), and chronic cutaneous lupus were investigated and excluded. Once the hypothesis of KLC was raised, acitretin 30 mg/day (approximately 0.3 mg/Kg/day) was introduced, with progressive improvement of erythema and pruritus in 90 days of treatment (Figure 6).

Discussion

Nekam's disease or KLC is a relatively rare disease, that was first described by Kaposi in 1886 as "lichen ruber moniliformis." However, in 1895, two patients with

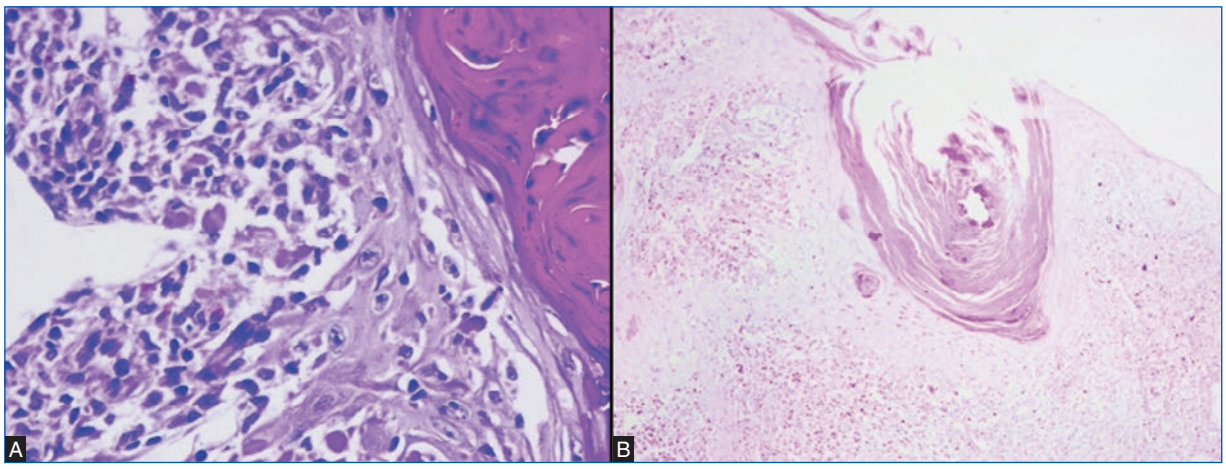

Figure 4. **A:** intense vacuolization of the basal layer (HE, ×400). **B:** large corneal stoppers (HE, ×100).

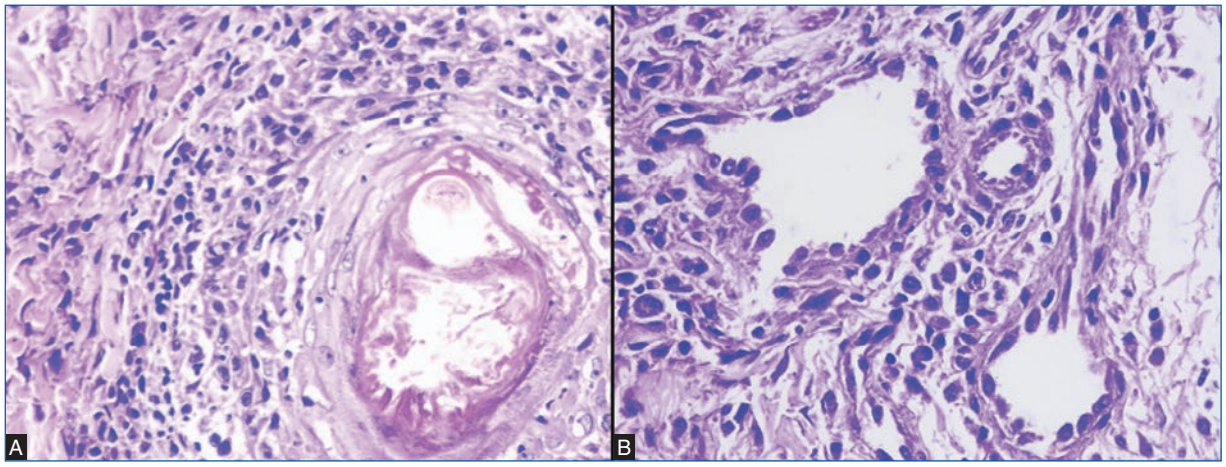

Figure 5. **A:** perifollicular inflammatory infiltrate, invading the follicle wall, with vacuolar degeneration of the basal layer (HE, ×400). **B:** infiltrate with plasma cells around dilated vessels and entombed endothelium (HE, ×400).

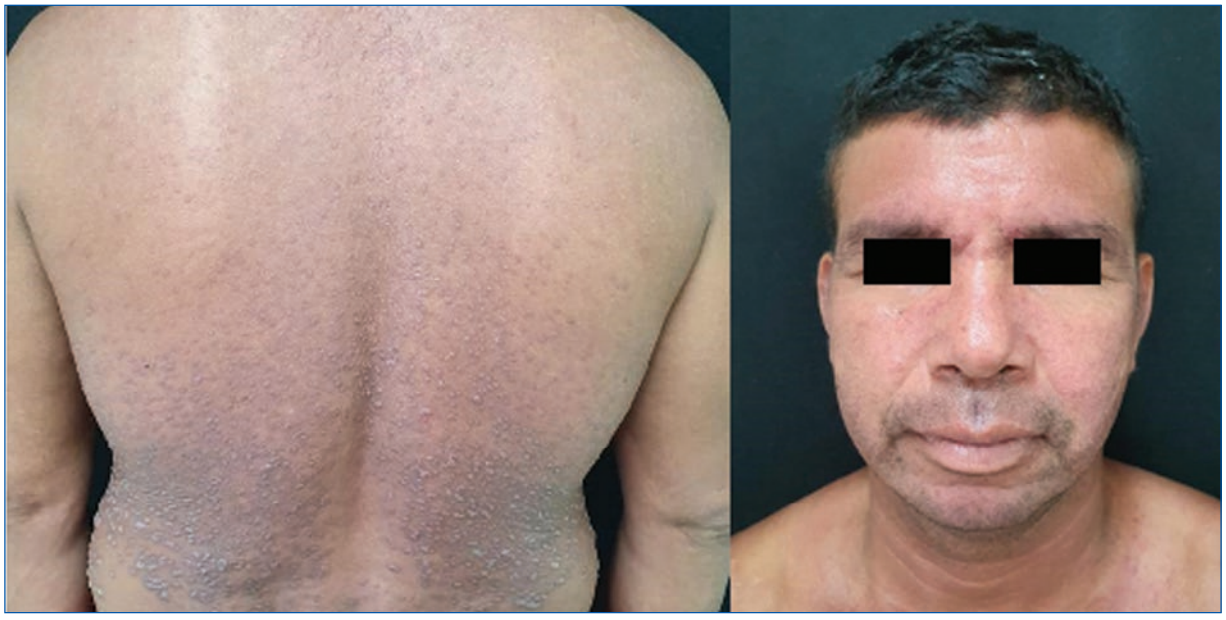

Figure 6. Improvement of trunk and face erythema and reduced lesion thickness after 3 months of continuous use of acitretin.

similar lesions were diagnosed with "lichen ruber acuminatum (verrucosus et reticularis)"[1]. In 1938, Nekam observed acrosyngeal hyperkeratosis in the case published by Kaposi, which caused the disease to be called lichenoid streaky porokeratosis, despite the absence of a horny lamella[2]. Since then, it has been reported under different nomenclatures, among them striated porokeratosis, verrucous and reticular lichen, lichenoid triceratosis and strieé lichenoid keratosis[3]. The widely used term KLC was introduced by Margolis et al. in 1972[2].

KLC is an acquired, chronic, progressive mucocutaneous dermatosis that occurs most commonly in adolescents and young adults, with a slight male predominance (1.35:1)[4,5]. It usually appears between the third and fifth decade of life, with a mean age of 35.6 years at diagnosis[6]. However, there are reports in children, some with a possible genetic association with an autosomal recessive pattern[7]. The mean time between onset and diagnosis was 9 years, with only 30% of patients being correctly diagnosed within 2 years of onset, 20% within 5 years, and 50% after more than 5 years[6].

The exact etiopathology of this disease remains unknown and no significant association with underlying diseases has been proven, but some factors such as trauma, autoimmunity, infections, drugs, infrared radiation, inflammatory diseases, and hematological malignancies have been reported concomitantly[6,8]. Some authors suggest an immunological basis in the epidermis, probably autoimmune[4]. Clinically, KLC is characterized by hyperkeratotic erythematous-violaceous papules and plaques in a linear or reticular pattern, arranged symmetrically mainly on the trunk and extremities[5,9]. Pruritus is a variable finding, being present in less than 20% of patients[10]. A mid-facial erythematous eruption, seborrheic dermatitis-simile, or rosacea-simile, as observed in our patient, may be present in 75% of cases[5,9]. Palmoplantar keratoderma may be evident in approximately 40% of patients[11].

Nail, oral, and genital involvement is frequently seen in adults, whereas alopecia and pruritus are frequent in children[8]. Nail dystrophy may be noted in 30% of cases[12], the most frequent changes include yellowish chromonychia, lamina thickening, and hyperkeratosis of the nail bed[5,8,9]. Oral manifestations, present in 50% of cases, include ulcers and recurrent aphthous lesions. As for genital lesions, keratotic papules may occur on the scrotum and penis, in addition to chronic balanitis and phimosis. Ocular involvement encompasses blepharitis, keratoconjunctivitis, anterior uveitis, and iridocyclitis, as the most common, sometimes leading to visual impairment[13].

Epidermal changes include hyperkeratosis, focal parakeratosis, especial/y in the follicular openings, irregular acanthosis with areas of atrophy, and corneal stoppers. Vacuolar degeneration of the basal layer is a frequent finding. A chronic inflammatory infiltrate usually consisting of lymphocytes, histiocytes, plasma cells, a few eosinophils, and numerous Civatte bodies (necrotic keratinocytes) is observed in the upper dermis. The lichenoid infiltrate is often centered around an infundibulum or acrosyringe[1,3,6,10,14].

Although there is no definitive laboratory test for the diagnosis of this entity, clinical and histopathological clues are sufficient to make the diagnosis[9].

For a long time, KLC was considered a variant of LP that evolved by antigen mimicry followed by epitope dissemination. Today, many authors consider it to be a distinct entity[2].

Other conditions may resemble KLC and should be differentiated, among them chronic cutaneous lupus erythematosus, pityriasis lichenoides, pityriasis rubra pilaris, psoriasis, porokeratosis and mycosis fungoides, including paraceratosis variegata and folliculocentric mycosis fungoides[10].

KLC is a therapeutic challenge, showing resistance to a variety of treatments including topical and systemic corticosteroids, antimalarials, dapsone, tetracyclines, methotrexate, and cyclosporine[1,4,6,9,15]. Varied results have been observed in psoralene with ultraviolet A radiation (PUVA), systemic retinoids, either etretinate alone or combined with PUVA or with narrow-band ultraviolet B radiation (NB-UVB), as well as topical calcipotriol and NB-UVB monotherapy. NB-UVB has proven to be more effective in treating children than adults[1]. Oral retinoids, isotretinoin and especially acitretin, given at a dose of 0.3-0.6 mg/Kg/day, have been shown to be the most effective option, with a rapid onset of action, in approximately 1-2 months. Flattening of the lesions is observed as early as the first month, with significant improvement expected in 4-6 months after starting treatment[6,8], similarly to we observed in our patient. A review of 30 patients diagnosed with KLC and treated with oral retinoids showed partial response in 20% and complete response in 36.6% of patients[6].

KLC is a difficult disease to diagnose, considering its clinical and histological similarity with other dermatoses and also its rarity or possible underdiagnosis, since the findings can be mistaken with other pathologies.

Although it has a benign course, lesions cause significant psychosocial damage, and effective therapeutic strategies should be sought despite the lack of consensus in the literature.

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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.

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CASE REPORT

Acute generalized exanthematous pustulosis associated with SARS-CoV-2 infection

Pustulose exantemática generalizada aguda associada a infecção pelo SARS-CoV-2

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Abstract

Acute generalized exanthematous pustulosis (AGEP) is characterized by the sudden onset of diffuse sterile pustules on an erythematous background. It is mainly caused by drugs and, clinically, it usually improves quickly after discontinuation of the causative agent. Viral and bacterial agents have also been reported as triggers. We present a case regarding a woman reporting flu-like symptoms, taking dipyrone, paracetamol, and azithromycin. A reverse transcriptase polymerase reaction (RT-PCR) test confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. After 2 days, she noted the onset of erythematous plaques covered by diffuse pustules. The negative patch test reinforced the viral infection as the possible causative agent.

Keywords: Acute generalized exanthematous pustulosis. COVID-19. SARS-CoV-2.

Resumo

A pustulose exantemática generalizada aguda (PEGA) é caracterizada pelo surgimento súbito de pústulas estéreis difusas sobre fundo eritematoso na pele. É causada principalmente por medicamentos e geralmente melhora rapidamente após a interrupção do agente causador. Agentes virais e bacterianos também já foram relatados como desencadeantes. Apresentamos um caso de uma mulher com sintomas gripais, em uso de dipirona, paracetamol e azitromicina. Um teste de RT-PCR confirmou a infecção por SARS-CoV-2. Após 2 dias, notou o aparecimento de placas eritematosas cobertas por pústulas difusas. O teste de contato negativo reforçou a infecção viral como provável agente causador.

Palavras-chave: Pustulose exantematosa aguda generalizada. COVID-19. SARS-CoV-2.

Introduction

Acute generalized exanthematous pustulosis is a rare disease characterized by the sudden onset of diffuse sterile pustules on an erythematous background[1,2]. It usually improves quickly after discontinuation of the causative agent, even though severe cases have been described. Viral and bacterial agents have also been reported as triggers[1-3], as well as rare additional

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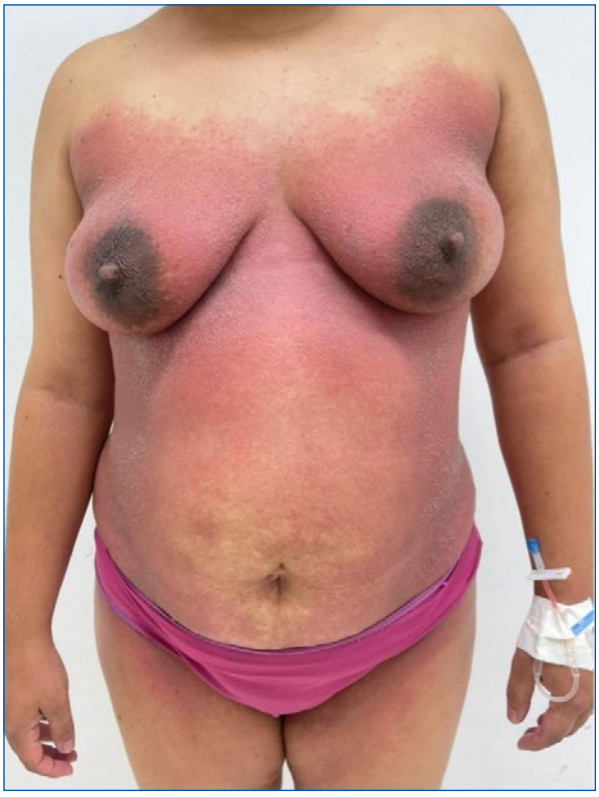

Figure 1. Erythematous plaques covered by small pustules in the trunk, mainly in the inter and submammary folds, breasts, abdomen, medial part of arms and internal side of thighs.

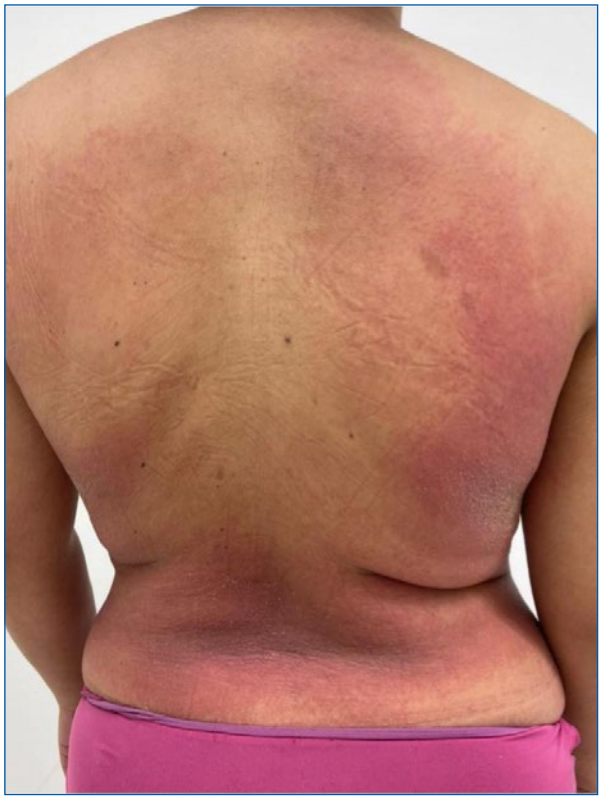

Figure 2. Erythematous plaques covered by small pustules in the medial part of arms and back.

causes, such as contact with mercury and spider bites[2]. However, the main triggering factors are drugs, such as antibiotics, hydroxychloroquine, terbinafine, diltiazem, and fluconazole. The period from drug exposure to the reaction onset is approximately 48 h, with antibiotics with an average of 24 h[2].

Case report

A 35-year-old women, mixed race, reported a flu-like condition for 3 days, taking dipyrone and paracetamol for symptom control. After 2 days, she was prescribed azithromycin due to a suspected SARS-CoV-2 infection, which was confirmed later through a PCR test. On the 3rd day of symptoms, erythematous plaques covered by small pustules appeared in her trunk, mainly in the inter and submammary folds, associated with local burning, and the exanthema soon progressed to the medial part of her arms, internal side of thighs, and back (Fig. 1 and 2). Azithromycin was discontinued, and she was hospitalized and started oral prednisone 40 mg/day, with an important improvement of lesions in the following 3 days.

Histopathology showed a subcorneal and intraepidermal pustular dermatosis, with severe edema in the papillary dermis and without eosinophils, compatible with the hypothesis of AGEP.

About 1 year later, the patient was called again for diagnostic elucidation. A patch contact test was conducted with the Brazilian Standard Battery of allergens and other suspected substances (dipyrone and acetaminophen, powder mixed with vaseline at 10%, and azithromycin, powder mixed with petrolatum at 5%) with a negative result for all the substances at the readings at 2 and 4 days, therefore reinforcing that SARS-CoV-2 infection could have been the potential triggering cause.

Discussion

Acute generalized exanthematous pustulosis is a neutrophilic disease which is related to a type IV immune-mediated hypersensitivity response. After exposure to the causative agent, antigen-presenting cells cause the activation of a specific cluster of differentiation (CD)—CD4 and CD8 T cells, which migrate to the dermis and epidermis, causing apoptosis of keratinocytes, formation of epidermal vesicles, chemotaxis

of neutrophils through interleukin 8, and activation and transformation of vesicles into sterile pustules due to a prevalent Th1 and Th17 profile[1-3].

Histological findings are characterized by intracorneal, subcorneal, or intraepidermal spongiform pustules with papillary dermis edema containing neutrophilic and eosinophilic infiltrates[1].

A patch test may be used to identify the cause of AGEP when the causative drug is not clear, but although the sensitivity of these tests in AGEP is around 50%, sensitivity depends on the culprit drug, and there are no reports of positive patch tests to azithromycin or dipyrone in this setting[1,2,4].

Skin manifestations of SARS-CoV-2 infection include perniosis, morbilliform, vesicular, or urticarial rash, vasculitis, and necrotic lesions[1,5]. To date, only two cases of AGEP triggered by SARS-CoV-2 infection, with no prior use of hydroxychloroquine, have been reported in the literature[1,5,6].

Although AGEP is not commonly related to viral agents, we cannot rule out the SARS- CoV-2 infection as the main trigger, mainly after the nonreactivity of the patch test.

There is a lack of robust evidence regarding skin manifestations related to SARS-CoV-2 infection. Few case reports describe the association of AGEP with SARS-CoV-2 infection. In most reports, the patients had previously used hydroxychloroquine.

Acknowledgment

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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.

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IMAGE IN DERMATOLOGY

Hyperpigmentation of the tongue as a clue to the diagnosis of Addison's disease

Hiperpigmentação da língua como uma pista para o diagnóstico da doença de Addison

Hudson D. Rezende[1,a], Carolina Z. Oliveira[2,b], Danielle Braga[3,c], Aline F. Loures[1,d], Letícia Logullo[1,e], Sandra L. M. Dinato[1,f] and Alexandra C. Toled[4,g]*

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A 12-year-old girl complaining of fatigue during the last 3 months also reported progressive darkening of the tongue followed by hyperpigmentation of the oral mucosa and the skin. On physical examination, a central macular brown-grey hyperpigmentation of the tongue was noticed (Fig. 1A). Dermoscopy showed irregular pigmentation surrounding the fungiform papillae (Fig. 2). Laboratory examination revealed low glucocorticosteroid serum level (3.6 µg/dL) and high adrenocorticotropic hormone (ACTH) 1.250 pg/mL, which confirmed the diagnosis of Addison's disease (AD). No other serum parameters were abnormal. After treatment with oral prednisone 7.5 mg/day both the tongue and the skin hyperpigmentation faded in 6 months (Fig. 1B).

Addison's disease is an uncommon condition that is frequently overlooked in clinical practice, yet truly life-threatening[1]. Affected individuals may show non-specific signs and symptoms, such as vomiting, unexplained weight loss, fatigue, malaise and generalized hyperpigmentation[1]. For patients whose clinical presentation is not complete, pigmentation of the tongue may allow an early diagnosis[2]. Hyperpigmentation results from melanogenesis stimulation due to increased production of opiomelanocortin[3], a prohormone that is the source of biologically active ACTH, and melanocyte-stimulating hormones involved in melanin synthesis[1,3,4].

Pigmentation of the oral mucosa has been observed in several different scenarios, such as physiologic conditions, metabolic disorders, use of medications or other exogenous substances[1,2,5]. Darkening of the tongue may be associated with either melanin deposition or external pigments and is frequently seen among darkly pigmented individuals, in the context of astringent mouthwash abuse, drinking dark tea and other caffeinated drinks, as well as heavy smoking habits[3,6].

Any patient with hyperpigmentation of the tongue should be evaluated for systemic medications (e.g., tetracycline, proton pump inhibitors, interferon, phenytoin, and hydroxychloroquine), inherited disorders (Peutz-Jeghers syndrome, von Reckling-hausen's syndrome), hemochromatosis, pernicious anemia and scleroderma[2,3,7,8].

According to Studdiford et al., oral cavity hyperpigmentation in AD is typically generalized, with patchy darkening of the inner surface of lips and buccal mucosa and also affects the gingival border and the

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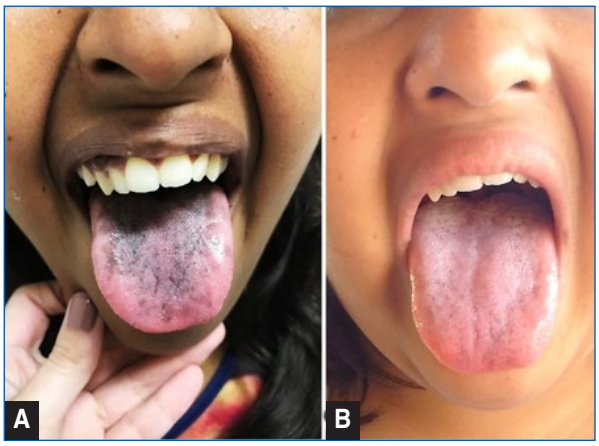

Figure 1. A: grayish brown hyperpigmentation of the tongue at first consultation. **B:** after treatment with oral glucocorticoids, both skin and mucosa returned to their original aspects.

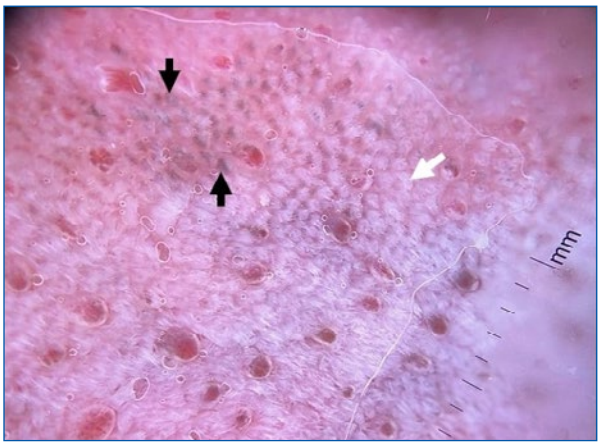

Figure 2. Tongue dermoscopy in Addison's disease: focal spots of brown pigmentation around the lingual papillae on the lateral aspect of the tongue (black arrows). White structures represent the tips of uninvolved papillae (white arrow); handheld dermoscopy.

tongue[3], as in the present case. As of yet, there is no data on the dermoscopy of hyperpigmented tongue in AD, but it may represent a complementary tool for such cases, as it may contribute to differentiating between the deposition of melanin and external pigments.

As suggested by Rosebush et al., the combination of fatigue and acquired diffuse pigmentation of the oral cavity has a great practical meaning since the former is virtually present in all patients with AD and the latter is an early, and highly specific feature of the disease[2]. Of note, patients with AD may exhibit isolated oral pigmentation long before skin changes are evident[9].

Finally, the diagnosis of AD may be tricky, especially when typical and systemic symptoms are not overt. By including AD as a possible diagnosis for mucocutaneous hyperpigmentation, the physician is more likely to recognize the diagnosis of AD earlier.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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.

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IMAGE IN DERMATOLOGY

Slowly progressive tumorous mass on the back

Massa tumoral lentamente progressiva no dorso

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A 72-year-old, who had had surgery and postoperative chemotherapy for breast cancer 20 years before, presented to the dermatology department with a nodule of the upper back, slowly enlarging for 12 years, that was creating discomfort and tension in the scapular area. This 5 cm large mass covered by violaceous skin infiltrated deeply into the subcutaneous tissue with no mobility (Fig. 1a, b). The patient was otherwise in good overall condition with no other symptoms or weight loss.

A computerized tomography scan of the whole body showed a tumor formation in the subcutaneous fat tissue

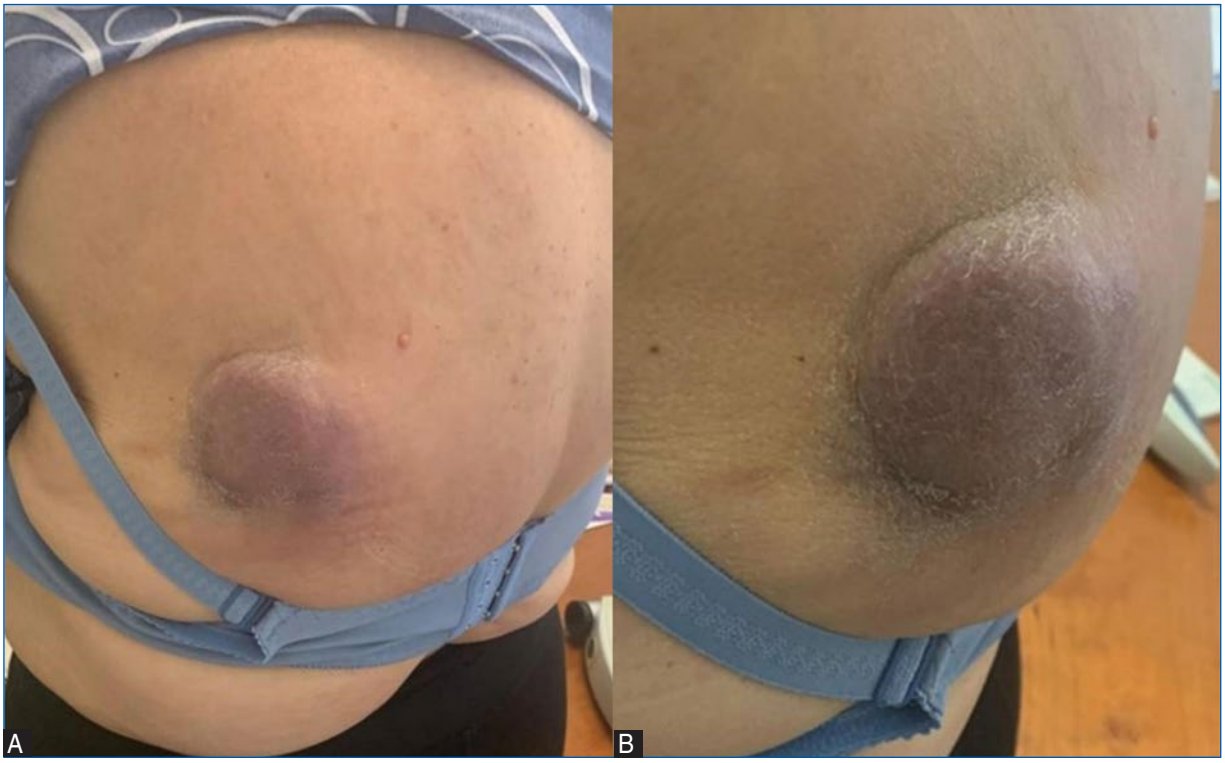

Figure 1. A, B: A skin nodule with a violet color, 5 cm in a diameter located in the area of the left scapula.

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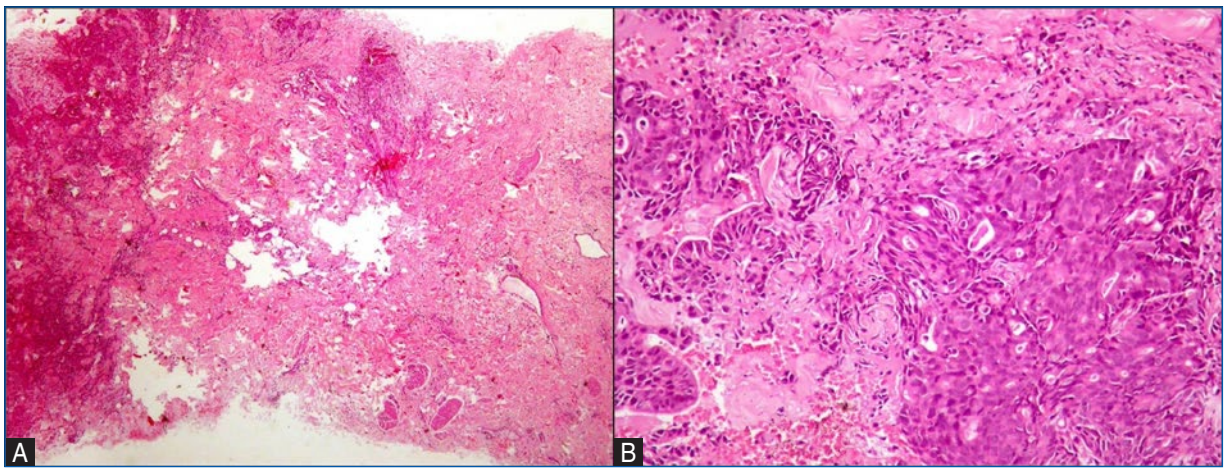

Figure 2. A: hematoxylin-eosin stained sections at 10, 20, **B:** 40× magnification, showing nests of tumor cells in the deep dermis and hypodermis with atypical cells, nuclear pleomorphism, and pronounced stromal reaction and desmoplasia.

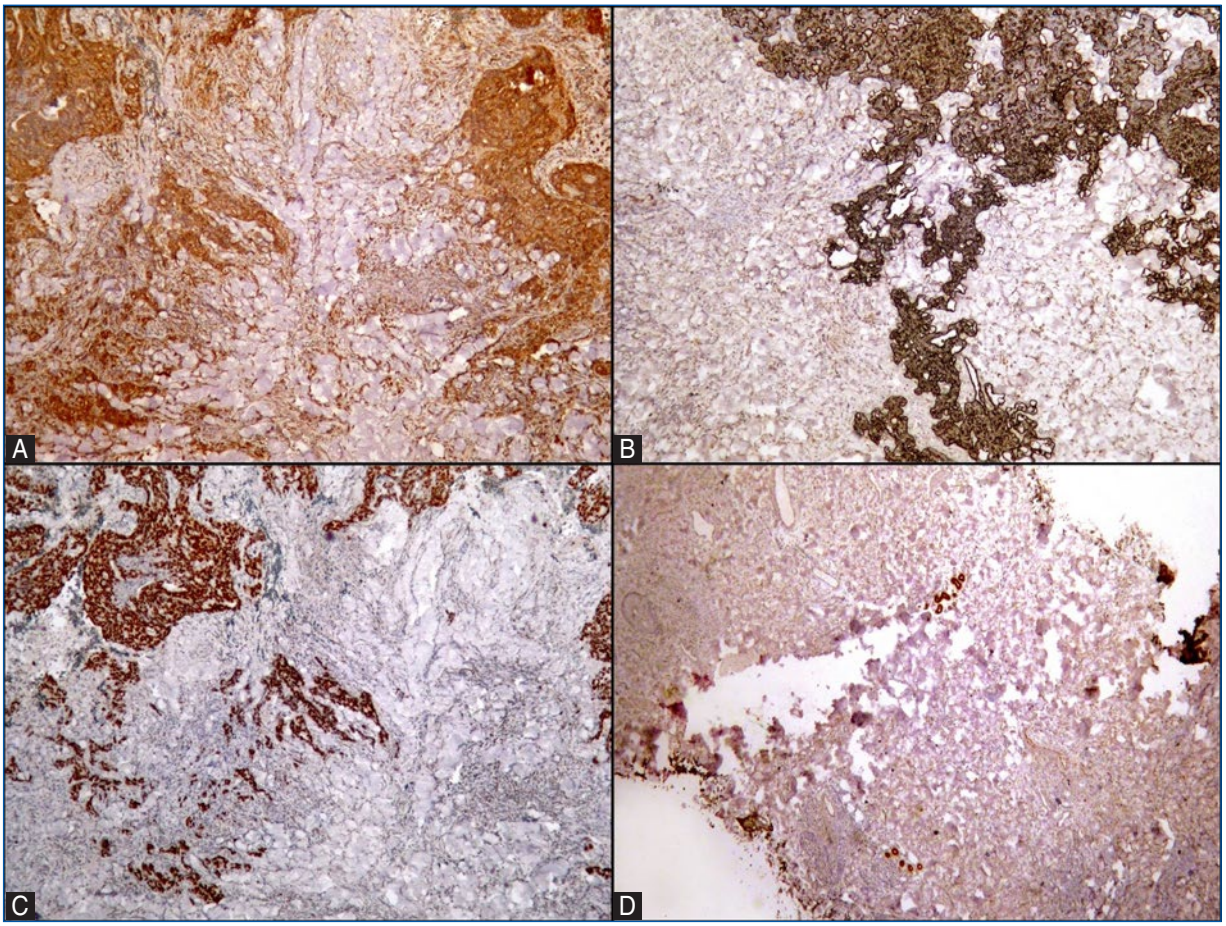

Figure 3. Immunohistochemistry showing atypical cells in the nests expressing: **A:** HER2 (+++), **B:** ER, **C:** GATA3 **D:** negative for CK-7.

of the chest wall on the left retroscapular region with satellite nodules in the proximity but no internal masses.

A "punch" biopsy from the middle of the tumor showed in the deep dermis and hypodermis, nests of tumor cells with cellular atypia, nuclear pleomorphism, and a pronounced stromal reaction and desmoplasia (Fig. 2a, b). Immunohistochemistry showed expression of human epidermal growth factor receptor 2 [HER2 (+++)], estrogen receptor (ER) and GATA3 (Fig. 3a-c) and no expression of cytokeratin 7 (CK7) (Fig. 3d) or nap sin A. The diagnosis of a giant cutaneous metastasis from poorly differentiated grade 3 ductal invasive carcinoma of the mammary gland was made. After the diagnosis, the patient was referred to oncology for further treatment.

Cutaneous metastases are a rare clinical finding and can sometimes be the first manifestation of an internal malignant tumor, or its recurrence. In women, skin metastases are most often observed from breast cancer and melanoma[1,2]. Actually, breast cancer is considered the most common type of tumor likely to metastasize to the skin[3]. Cutaneous metastasis from breast cancer metastases can present as nodules and rarely as bullae, plaques and areas of alopecia[4], suggesting different dermatological conditions[4].

The evolution of skin lesions is also diverse, and the lack of rapid progression over the years, as in the present case, should not reassure clinicians nor suggest other benign lesions, such as lipoma.

Ethical disclosures

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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.

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Use of rituximab in pemphigus vulgaris/foliaceus patients during COVID-19 pandemic

Utilização de rituximab em doentes com pênfigo vulgar/foliáceo durante a pandemia COVID-19

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Dear Editor,

The SARS-CoV-2 pandemic has raised safety concerns in pemphigus vulgaris/foliaceus (PV/PF) patients on systemic immunosuppressants. Rituximab (RTX) induces a prolonged B-cell depletion, which was initially associated with severe COVID-19 disease[1]. Moreover, the approval of SARS-CoV-2 vaccines brought into question issues about efficacy, safety, and timing of vaccination in individuals receiving anti-CD20 monoclonal antibodies.

We aim to share the experience of our center regarding COVID-19 disease and vaccination in patients with PV/PF on RTX.

A retrospective analysis of the patients who received at least one infusion of RTX from January 2020 to March 2022 was performed. Data on SARS-CoV-2 vaccination and disease was obtained after consulting the hospital's clinical platforms. Secondarily, a brief review of the literature on the incidence and severity of COVID-19 in patients with PV/PF under RTX and their vaccination was carried out.

In our Dermatology department, from January 2020 to March 2022, seven patients did at least one RTX infusion for the treatment of PV/PF. All patients were female, with a mean age of 46.6 years. During this period, three patients developed COVID-19, all with mild disease. Six patients were vaccinated, and one patient declined vaccination. Two of the vaccinated patients received the vaccine at least 1 month before the beginning of the treatment and four of them were vaccinated more than 3 months after. Regarding the three patients that developed COVID-19, one had received two doses of the SARS-CoV-2 vaccine 5 months prior to the treatment, one had completed the two-dose schedule 3 months after the last RTX infusion, and the last one was unvaccinated. During the analyzed period, none of the patients experienced PV/PF flare due to SARS-CoV-2 vaccination or infection.

RTX induces prolonged B-cell depletion and decreased antibody production, leading to a higher infection susceptibility. In SARS-CoV-2 infection, the host's immune response is crucial for the evolution of the disease, with immunosuppression being considered an independent risk factor for severe disease. However, recovery from COVID-19 may not be determined exclusively by the development of neutralizing antibodies. In fact, a recent study showed that 11 out of 14 patients on RTX who recovered from COVID-19 had no measurable anti-SARS-CoV-2 antibodies titers[2].

The incidence and severity of COVID-19 in patients with PV/PF under RTX have also been investigated. However, there are few studies and conflicting results. For example, a recent analysis including 18 patients diagnosed with PV/PF concluded that the use of RTX was associated with five times higher incidence of the disease[3]. Another study that included 620 patients with

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PV/PF found that the risk of hospitalization decreases each month after the administration of RTX[4]. On the other hand, a larger analysis with a sample of 1236 patients with PV/PF concluded that the use of immunosuppressants, including RTX, was not associated with disease severity[5]. A smaller study of 211 patients showed similar results[6].

In our sample, the use of RTX does not appear to be associated with severe illness since the three cases of COVID-19 were mild. In fact, while it is well established that RTX leads to a decrease in the humoral response lasting beyond 6 months, a possible protective role has been hypothesized. RTX can reduce the so-called "cytokine storm" responsible for severe disease, by decreasing the systemic pro-inflammatory state.

At the time of SARS-CoV2 vaccine approval, the only available recommendations for vaccination of patients on RTX were those of inactivated vaccines such as Influenza or tetanus[7]. However, the emerged SARS-CoV-2 vaccines are not inactivated, but mRNA or viral vector based. In these patients, vaccination timing is important and, according to the literature, vaccine humoral response recovery seems to occur six months after the last administration of RTX[8,9]. Additionally, it has also been demonstrated that cell-mediated immunity is robust, which can counterbalance an eventual decrease in the humoral response to vaccination[8,9].

In fact, the ideal timing for vaccination after treatment with RTX is not yet fully established and the only precise recommendations are from the American College of Rheumatology, suggesting vaccine administration 2 to 4 weeks before the beginning of a treatment cycle[10]. Furthermore, the measure of CD19 B-cells may be a useful tool to define vaccination boosters and RTX dosing[10].

In conclusion, the incidence and severity of COVID-19 among patients on RTX, especially those with autoimmune blistering disorders, have not been fully characterized. Although the vaccination of these patients is safe and effective, regarding the predictable robust cell-mediated response, the optimal timing for COVID-19 vaccination is not yet established. The increasing emergence of new pandemics, along with the wide use of biotechnological drugs, will certainly be a challenge in future clinical practice. Thus, it is important to better understand the real impact of these drugs on a patient's immune response, regarding not only the modification of the natural history of the disease but also, and most importantly, the need for vaccination schedule adjustment.

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Conflict of interests

The authors have no conflicts of interest to disclose.

Ethical disclosures

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LETTER TO THE EDITOR

Nitrosamines in antihypertensives, metformin and ranitidine as cofactors for melanoma and development of other cancers. Expert group opinion

Nitrosaminas em anti-hipertensivos, metformina e ranitidina como cofatores para melanoma e desenvolvimento de outros cancros. Artigo de opinião

Georgi Tchernev[1], Simona Kordeva[2], Viktor Marino[3], Ilia Batashki[4], Atanas Batashki[5], and James W. Patterson[6]*

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To stress the issue of sartans as a possible cause of various cancers as already reported in the case "Insights into the development of lentigo maligna and dysplastic nevi: Spotlight on the possible relation with sartans, thiazides and nitrosamines" published in vol no. 3, 2022 of this journal[1], we want to inform that there is currently no clarity on the part of regulators as to whether (1) nitrosamines (as an additional contaminant) and/or (2) the active substance of angiotensin receptor blockers are responsible for the "procarcinogenic" effect of these drugs[2].

Nevertheless, the relationship between the sartan intake and all types of neoplasms seems increasingly real, and its statistical significance has become more pronounced over the years[3].

A number of experimental data initially shed some light on the use of the sartans and the risk of melanoma as early as 2018/2019, but unfortunately did not contain definite information on whether the active substance used in their research included nitrosamines or not.

Clinical follow-up on the subject over the last decade has categorically supported the experimental data and again favors a serious risk of developing melanoma after taking the sartans. The statistics in these studies are also supportive, but still,

there is no evidence of the presence or absence of potential contamination with nitrosamines.

According to the data in the world literature, nitrosamines found so far in the sartans, and valsartan, in particular, could be up to three and according to various models for calculating the risk of cancer, the theoretical risk would be increased from 3 to 4 times[4].

Isolated publications in the world literature have focused the scientific community's attention not only on the risk of potential contamination of affected batches of the sartans with nitrosamine but also emphasize the additional "aggravation" of this risk (of melanomas, for example) due to concomitant use of thiazide diuretics[5]. By acting in a similar way (proven contamination by nitrosamines in the thiazide itself, or in combination with the sartans), or in a different pathogenetic way (i.e., photosensitization), thiazide diuretics increase the risk of developing both melanocytic and nonmelanocytic skin cancers[5].

In 2022, Pfizer surprisingly withdrew the Angiotensin-converting enzyme (ACE) inhibitor quinapril, the diuretic

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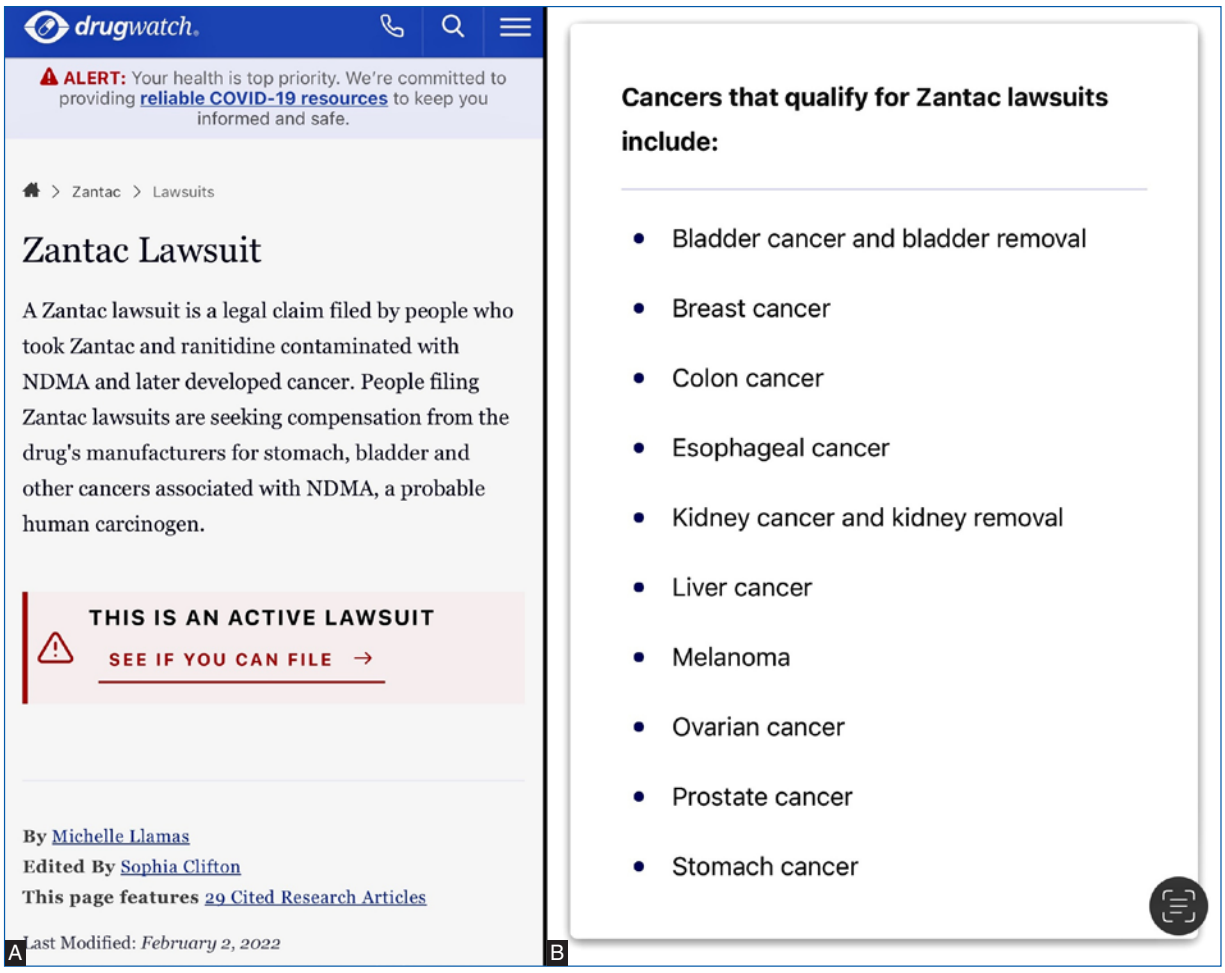

Figure 1. Drugwatch/FDA's list of compensatory claims for patients taking ranitidine/Zantac (contaminated with nitrosamines). **A**: what is a Zantac lawsuit. **B**: cancers that qualify for Zantac lawsuits.

drug hydrochlorothiazide, and the combination products containing these two ingredients due to an N-nitroso quinapril concentration well above the so-called acceptable daily intake level[6].

The contamination of metformin, ranitidine, and rifampicin with nitrosamines has been repeatedly demonstrated over the years, and several batches of these agents have been withdrawn from the market.

Polymorbid patients with diabetes who are treated with metformin could similarly be at risk for the development of melanoma or other tumors due to contamination with N-nitrosodimethylamine (NDMA)—the same ingredient found in sartans and ranitidine. Metformin is often prescribed in parallel with sartans and thus further increases the risk of developing melanoma or other skin neoplasms or preneoplastic conditions[5,6].

The nitrosamine NDMA found as a contaminant in ranitidine has been associated with an increased risk of developing melanoma since 2021, according to official DRUG WATCH/FDA data[7], although there is no evidence of even a single publication in the world scientific literature about that relationship.

By February 2022, however, melanoma was again included in the DRUG WATCH/FDA's list of compensatory claims for patients taking ranitidine/Zantac (contaminated with NDMA), but only a few months later it was removed from the bulletin without any explanation (Fig. 1a, 1b)[8]. It is curious that, despite the growing number of melanomas in the world literature after taking potentially NDMA-contaminated sartans, DRUG WATCH/FDA does not include them in the compensation claims of those affected. On the contrary, they were excluded from this group for Zantac on May 5, 2022 (whereas they were initially included on February 2, 2022), despite the growing number of scientific publications favoring the pathogenetic link between NDMA and the development and progression of melanoma.

After an in-depth analysis of the published data (DRUG WATCH), it could be reasonably assumed that, in the face of the FDA/European Medicines Agency, the regulatory authorities should have unpublished data sheets for self-reported side effects that prove or are at least highly indicative for the presence of a link between ranitidine intake and the development of melanoma.

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.

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