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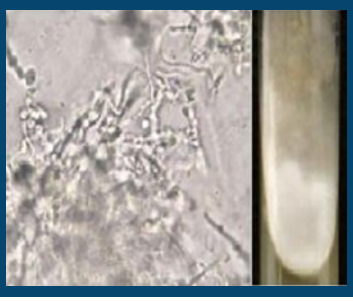

In this issue:

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Cover design: Fusarium spp. A: elongated and ovoid macroconidia, some microconidia with the same shape as macroconidia, presenting pink refringence and white colony with a white reverse and yellow and pink pigmentations. B: fusiform macroconidia and beige colony with brown reverse, filamentous appearance. C: microconidia grouped in "false heads" and white colony with salmon reverse. D: many oval and pyriform microconidia, some fusiform macroconidia and loose and chained chlamydoconidia, a white colony with dark brown reverse. (Source: Mont'Serrat Laboratory).See article J.C. Lara et al. in this issue

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

NOVO
EFFACLAR H ISO-BIOME

UMA FÓRMULA DE CUIDADO COMPLETA

Para pele com tendência acneica sob tratamento
Apazigua e hidrata a barreira cutânea e atua no microbioma

H ISO-BIOME melhora a qualidade de vida do doente em 44%

0.2% *AQUA POSAE FILIFORMIS** *
REEQUILIBRA O MICROBIOMA

ÁGUA TERMAL + NIACINAMIDA
ACALMA E REDUZ A INFLAMAÇÃO

VITAMINA B5*
GLICERINA E ESQUALANO
REPARA E HIDRATA

PROCERAD*
REDUZ AS MARCAS

0.25% EXTRATO DE ORELLANA*
REDUZ A HIPERQUERATINIZAÇÃO E
REGULA A PRODUÇÃO DE SEBO
REDUZ A VIRULÊNCIA DA C.ACNES

*NOVO INGREDIENTE

91% REFERE QUE SENTE A PELE CONFORTÁVEL[1]

98% REFERE QUE A APLICAÇÃO É FÁCIL E CALMANTE[1]

-66% SECURA[2]

-71% DESCAMAÇÃO[2]

-27% ERITEMA[2]

1. 55 indivíduos com pele seca na face sob tratamento com Isotretinoína (Roaccutane). Aplicação do produto na face duas vezes ao dia durante 4 semanas.
2. Estudo clínico sob controlo dermatológico com 44 indivíduos em tratamento EPIDUO com rotina cosmética não eficaz no controlo da sensibilidade da pele durante mais de 1 mês; estudo durante 28 dias. Avaliação da QoL pelo dermatologista

LA ROCHE-POSAY. A EXIGÊNCIA DERMATOLÓGICA.

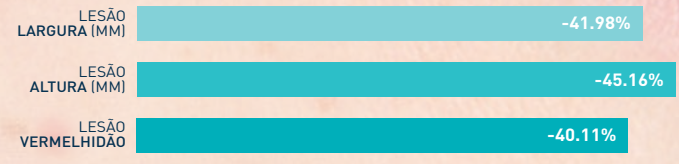
CeraVe
DEVELOPED WITH DERMATOLOGISTS

SERÁ POSSÍVEL INTERROMPER O CICLO DA ACNE SEM ALTERAR A BARREIRA CUTÂNEA?

CERAMIDAS 3 ESSENCIAIS

AVALIAÇÃO DERMATOLÓGICA
Em apenas 3 dias, 40% de REDUÇÃO nas LESÕES INFLAMATÓRIAS e VERMELHIDÕES

SEGUIMENTO LESÕES INDIVIDUAIS – DIA 3



Todas as alterações desde a base são significativas p<0.001

A disrupção da barreira cutânea e a diminuição de ceramidas na pele estão associadas à manifestação da acne.[1] **A CeraVe apresenta o Gel de Limpeza Controlo de Imperfeições e o Gel Controlo de Imperfeições,** formulados com 2% de Ácido Salicílico, para ajudar a desobstruir os poros e reduzir as lesões inflamatórias da acne – com 3 ceramidas essenciais, para reparar a barreira cutânea.

3 CERAMIDAS ESSENCIAIS | TESTADO EM PELE ALÉRGICA | SEM PARABENOS | SEM FRAGRÂNCIA | NÃO COMEDOGÉNICO

SIMULAÇÃO DE ACNE LEVE A MODERADA NA MODELO.

REFERENCE: 1. Yamamoto A, Takenouchi K, Ito M. Impaired water barrier function in acne vulgaris. *Arch Dermatol Res.* 1995;287(2):214-218.

CVE.G.P.0621

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

VICHY
LABORATOIRES

LIFTACTIV SUPREME
HA EPIDERMIC FILLER

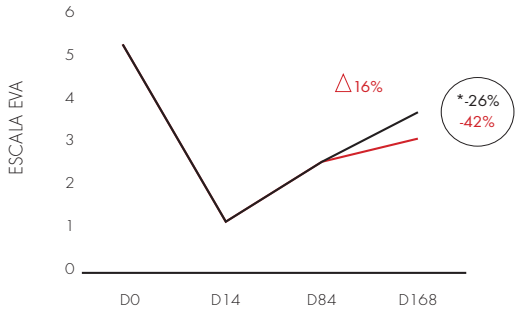
COMPENSA 100% DA PERDA DIÁRIA DE ÁCIDO HIALURÓNICO[1]

1,5% ÁCIDO HIALURÓNICO + VITAMINA Cg + PÉPTIDOS + ÁGUA VULCÂNICA VICHY

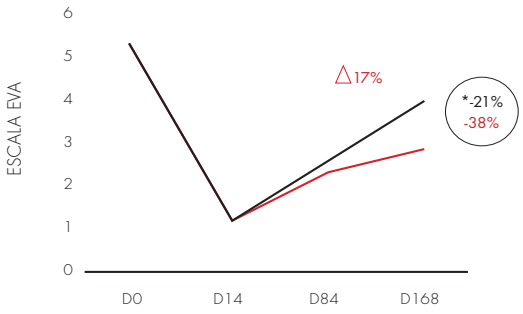
ESTUDO CLÍNICO PÓS-TOXINA BOTULÍNICA[2]

RESULTADOS SIGNIFICATIVOS EM **RÍDULAS** E NO **CONTORNO OCULAR**

RÍDULAS



RUGAS NO CONTORNO OCULAR



A: Injeção facial de toxina botulínica + Sérum Liftactiv HA Epidermic Filler

Controlo: Injeção facial de toxina botulínica

INDICAÇÕES
ROSTO
E CONTORNO OCULAR

- Prevenção e tratamento de sinais de idade
- Complemento de procedimentos estéticos

TESTADO SOB CONTROLO DERMATOLÓGICO E OFTALMOLÓGICO
HIPOALERGÉNICO - APTO PARA PELE SENSÍVEL - SEM FRAGRÂNCIA

1. Baseado na concentração de Ácido Hialurónico da fórmula, quando aplicada 2/dia.
2. Avaliação clínica, 63 mulheres. Aplicação 2/dia de Liftactiv Supreme HA Epidermic Filler + UV-Age Daily 1/dia, VS aplicação UV-Age Daily 1/dia, 6 meses. *significativo

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ORIGINAL ARTICLE

Teledermatology and the COVID-19 pandemic: experience from a Portuguese center

Teledermatologia e a pandemia covid-19: experiência de um centro português

Miguel Santos-Coelho[a], Joana A. Barbosa[b], Mafalda Pestana[c], Margarida B. Caldeira[d], Maria J. Paiva-Lopes[e], and Joana Cabete[f]

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Abstract

Introduction: In order to maintain assistential activity while ensuring social distancing and mobility restrictions imposed during the COVID-19 pandemic, the Dermatovenereology Department of Hospital de Santo António dos Capuchos implemented an asynchronous teledermatology platform based on e-mail and smartphones. This study aims to evaluate its application to urgent outpatient and inpatient consultations while considering its benefits and limitations. **Methods:** All written communications received via e-mail or smartphone between April 1, 2020 and April 31, 2021 were reviewed. Data was evaluated and statistical analysis was made using SPSS Statistics 25® software. **Results:** We reviewed 471 referrals (329 for outpatient and 142 for inpatient urgent consultations). E-mail was the most used platform (68.8%) and most referrals were composed of clinical information and clinical images (70.3%). Only 29% of these contained adequate clinical information and clinical images simultaneously. The majority of referrals received a response by a dermatologist in less than 24 hours (89%) and conversion to in-person evaluation was made in 58% of cases. The average time for in-person evaluation after triage was 0.25 days for inpatients and 4 days for outpatients. **Conclusion:** The COVID-19 pandemic hastened teledermatology implementation in order to maintain good healthcare. This study demonstrates that these platforms where wildly accepted by healthcare professionals and patients and remote consultations were possible in a significant percentage of cases. Teledermatology struggles with its own limitations and can never fully replace in-person evaluation, but can present itself as a useful tool in daily practice.

Keywords: Teledermatology. COVID-19. Pandemic.

Resumo

Introdução: Com o objectivo de manter a actividade assistencial numa altura em que o distanciamento social e as restrições de mobilidade entre hospitais consequentes à pandemia COVID-19 se apresentavam como fundamentais, o departamento de Dermatovenereologia do Hospital de Santo António dos Capuchos implementou uma plataforma assíncrona de teledermatologia baseada em e-mail e smartphones. Este estudo pretende avaliar a sua aplicação a consultas de urgência de

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ambulatório e internamento, dando destaque aos seus benefícios e limitações. **Métodos:** Todas as comunicações escritas recebidas por e-mail ou smartphone entre 1 de Abril de 2020 e 31 de Abril de 2021 foram analisadas. Os dados foram avaliados e foi realizada análise estatística com recurso ao software SPSS Statistics 25®. **Resultados:** Foram analisadas 471 referenciações (329 consultas urgentes de ambulatório e 142 consultas urgentes em internamento). O e-mail foi a plataforma mais usada (68.8%) e a maioria das referenciações eram compostas por informação clínica escrita e imagens clínicas (70.3%). Apenas 29% destas continham, em simultâneo, informação clínica e imagens clínicas adequadas. A maior parte dos pedidos recebeu uma resposta por um dermatologista em menos de 24 horas (89%) e, em 58% dos casos, foi efectuada uma conversão a consulta presencial. O tempo médio para uma consulta presencial após triagem foi de 0.25 dias para consultas em internamento e 4 dias para consultas de ambulatório. **Conclusão:** A pandemia COVID-19 acelerou a implementação da teledermatologia de modo a assegurar a manutenção de bons cuidados de saúde. Este estudo demonstrou que estas plataformas foram amplamente adoptadas por profissionais de saúde e doentes e a realização de consultas remotas foi possível numa percentagem significativa de casos. A teledermatologia apresenta várias limitações e nunca poderá substituir integralmente uma avaliação presencial, podendo ser, no entanto, uma ferramenta útil no dia-a-dia.

Palavras-chave: Teledermatologia. COVID-19. Pandemia.

Introduction

In March 2020, the World Health Organization classified the SARS-COV2 virus outbreak as a pandemic event. During the following weeks and months, hospitals and health services were overwhelmed with COVID-19 patients, and society itself went through major changes in order to (try to) contain the virus.

Months before the arrival of the first vaccines, personal protective equipment, frequent hand disinfection, social distancing, and mobility restrictions were the only available means to limit viral spreading. The Dermatovenereology Department of Hospital de Santo António dos Capuchos (HSAC) in Lisbon is in a unique situation in Portugal as it is responsible for all inpatient consultations and urgent outpatient evaluations in Centro Hospitalar Universitário de Lisboa Central (CHULC). Besides HSAC, the Center also encompasses Hospital de São José (HSJ), Hospital Curry Cabral, Hospital Santa Marta, Hospital Dona Estefânia, and Maternidade Alfredo da Costa.

In order to maintain assistential activity while ensuring social distancing and mobility restrictions imposed between hospitals, teledermatology platforms were employed. These can be defined as the use of electronic communications applied to dermatology to exchange medical information between remotely located health care professionals[1].

In order to accomplish this, an e-mail address hosted by CHULC's private network was created and a smartphone was made available to all department physicians. The latter was used both for accessing the previously mentioned e-mail account and also to receive short message services (SMS) and messages through encrypted communication services (such as Whatsapp®). Communication through both of these methods was made available to all physicians in CHULC.

The General Data Protection Regulation was followed in all processes, as patients gave consent to clinical image taking and sharing between medical professionals and patient's identification relied only on the hospital's patient ID number (which can only be accessed by medical professionals). Regarding the use of third-party software, consent from patients was also obtained previously; the use of encrypted end-to-end solutions meant that internet service providers, application service providers or any other entity were unable to access information that was only available to the sender and receiver (both medical professionals).

This study aims to evaluate the use of teledermatology methods in CHULC during the COVID-19 pandemic, with emphasis on type and quality of received information, response timing by physicians, and conversion to in-person evaluation.

Methods

A retrospective study of all inpatient and urgent outpatient consultations using teledermatology platforms during a 13-month period was conducted.

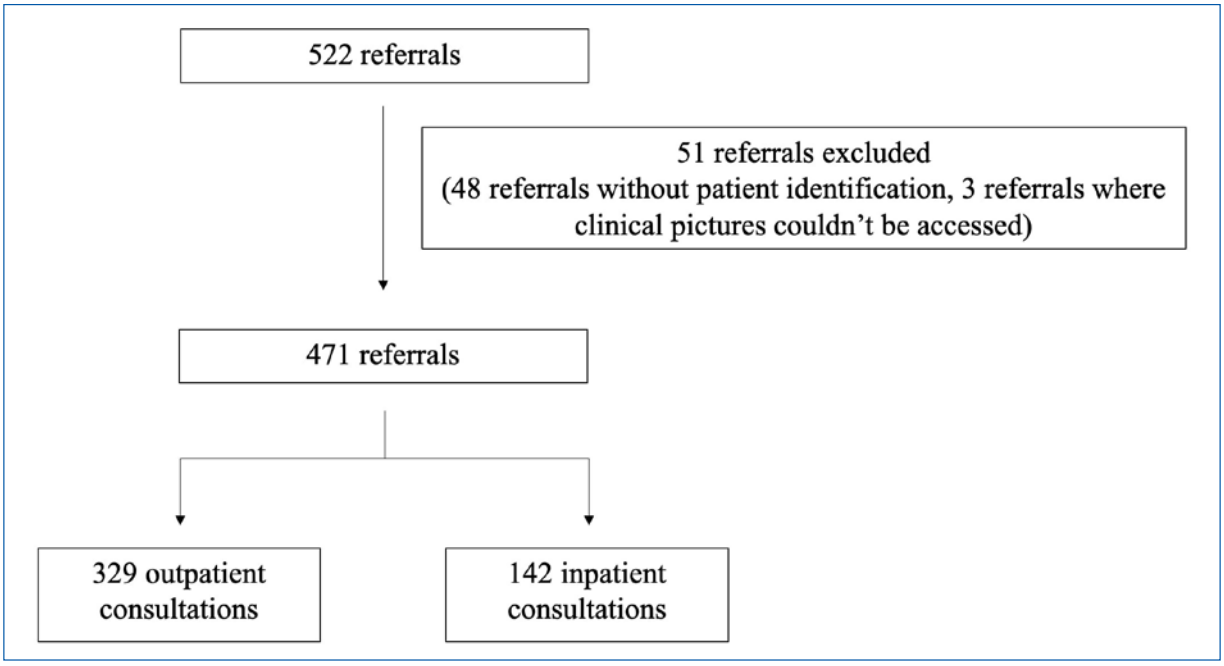

Figure 1. Referrals received.

All written communications received via e-mail or smartphone between April 1, 2020 and April 31, 2021 were reviewed. Those containing inpatient and urgent outpatient consultations were included. Exclusion criteria were lack of patient identification and the inability to access sent clinical images.

Clinical information was evaluated regarding essential anamnesis and other relevant data. Clinical images were analyzed based on framing, contrast, lighting, color, and sharpness. Data that enabled medical interpretation and decision-making (as defined by a panel of four physicians) was classified as "adequat". and the remaining as "inadequat".

Results were analyzed by SPSS Statistics 25®software.

Results

The inclusion criteria were met in 522 referrals and 51 cases were then excluded. Of the remaining 471 referrals, 329 (69.9%) were urgent outpatient consultations and the remaining 142 (30.1%) urgent inpatient consultations (Fig. 1). The distribution of referrals during the 13-month period is shown in Figure 2.

Referred patients had an average age of 53.7 years (1 month–96 years) and 237 (50.3%) were male. Subgroup analysis revealed an average age of 48 years (2 months–96 years) and of 67 years (1 month–94 years) for outpatients and inpatients, respectively.

Most referrals were received through e-mail (324 [68.8%]) and the remaining through encrypted smartphone apps (147 [31.2%]).

The majority of inpatient referrals originated from the Internal Medicine Wards (Fig. 3); the Emergency Department in HSJ was the most common source for urgent outpatient consultation referrals (Fig. 4).

Regarding content, the majority of inpatient and outpatient referrals (331 [70.3%]) were composed of written clinical information accompanied by clinical pictures (Fig. 5); "adequat". clinical information and clinical images were only present simultaneously in 96 cases (29%) (Table 1).

All other cases, composed only of written clinical information or clinical pictures, were further supplemented with additional data received by e-mail/message and/or phone calls through the Centro Hospitalar's private network. In this subgroup, 30% and 73.64% of first received referrals were classified as containing "good qualit". data, respectively (Table 2). Given that subsequent written information and clinical pictures were obtained after feedback from a dermatologist, this data was not evaluated in this study.

The majority of all referrals (419 [88.9%]) received a response by a dermatologist in less than 24 hours and this was also the case for subgroup analysis (Table 3). Conversion to in-person evaluation was made in 273 cases (58%), encompassing most outpatient referrals (230 [69.9%]) but less than a third of inpatient

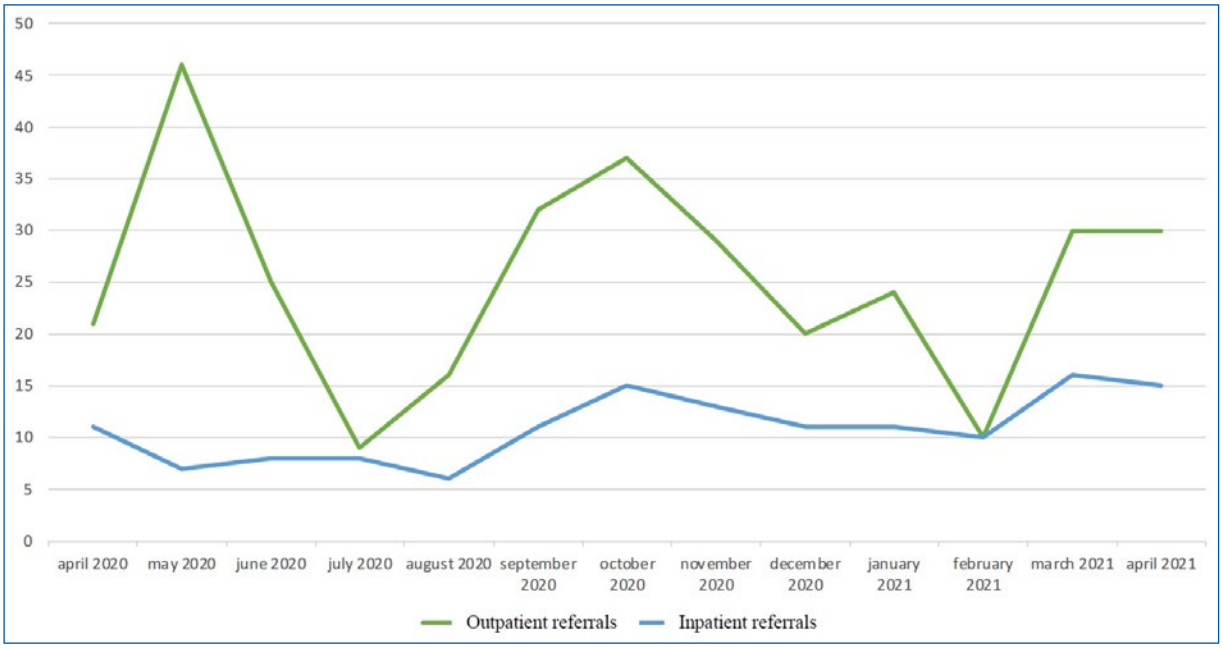

Figure 2. Distribution of referrals during a 13-month period.

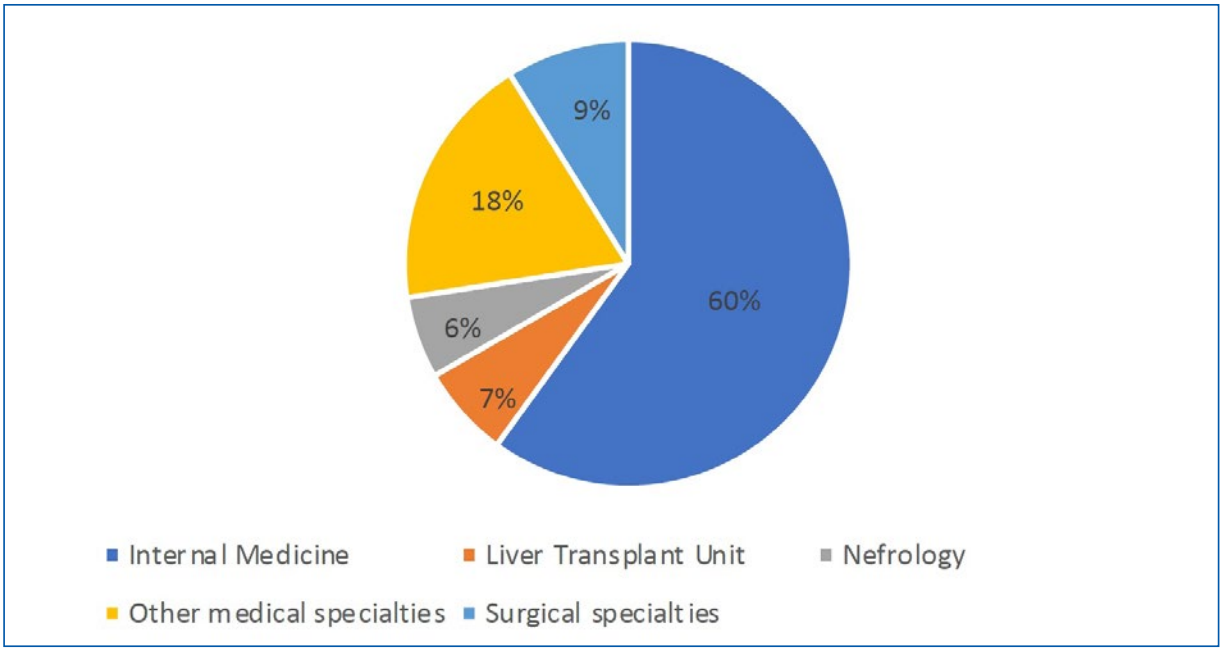

Figure 3. Origin of inpatient referrals.

referrals. The average time for in-person evaluation after triage was 0.25 days for inpatients and 4 days for outpatients (Table 4).

Discussion

Teledermatology care can be divided into three main platforms: synchronous (real-time), asynchronous (store and forward), and mixed (a fusion of the previous two)[2]. The Dermatovenereology Department of HSAC implemented an asynchronous platform based on e-mail and smartphones.

These methods of communication were rapidly made available and implemented in Centro Hospitalar Lisboa Central. The e-mail was the preferred method of referral for urgent consultations; we believe that widespread

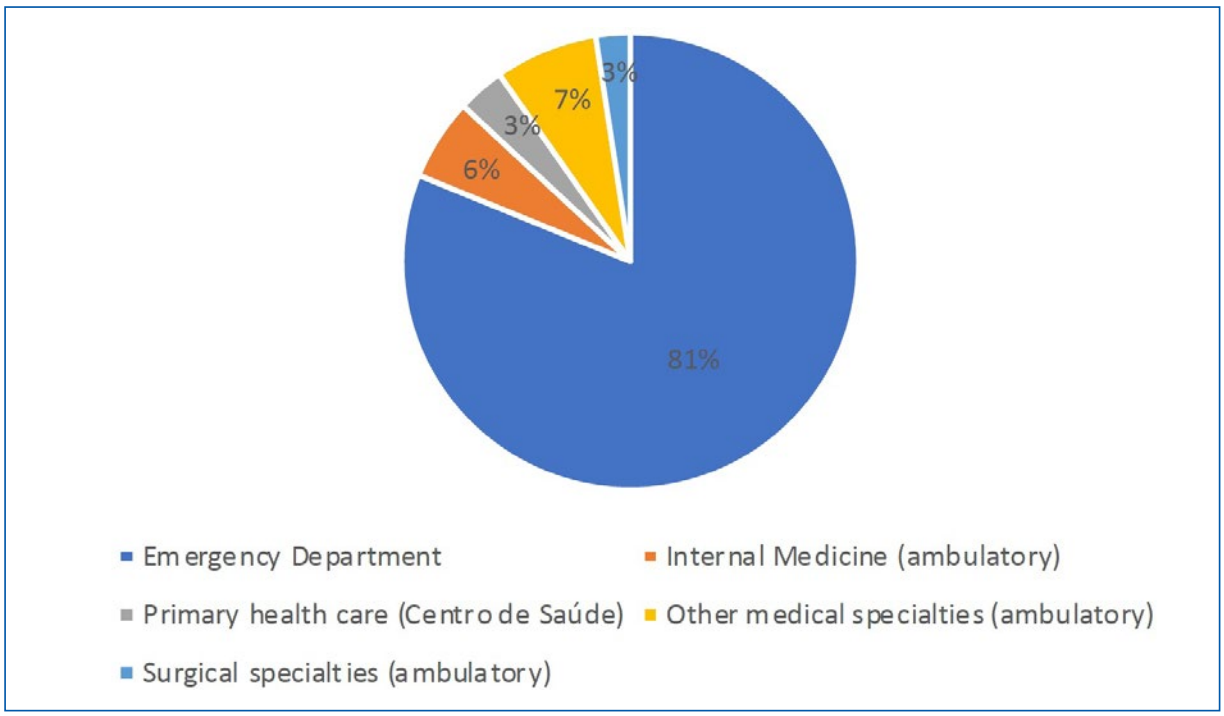

Figure 4. Origin of outpatient referrals.

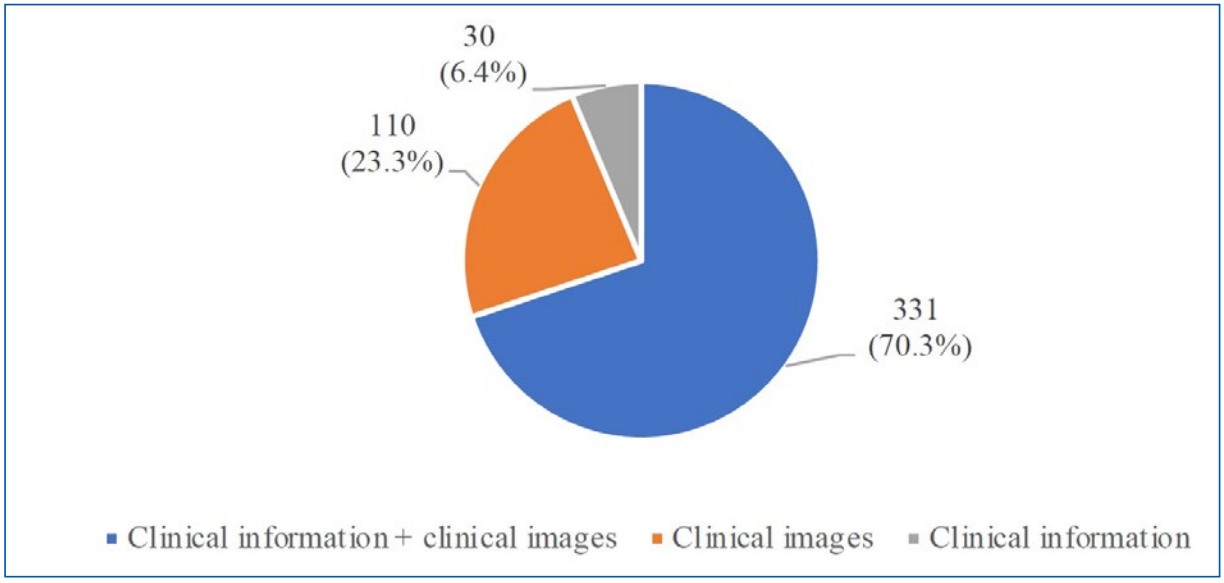

Figure 5. Type of data received in referrals.

availability, lack of need for specific equipment (i.e., smartphone, apps), secure integration in the hospital's network, and the use of work credentials instead of personal ones (i.e., private phone number) contributed to this fact.

Even though these were effective means of data transfer, lack of integration with the software used throughout CHULC were a difficult challenge to overcome. The constant need of switching between software (and operative systems when it came to smartphone usage) revealed itself as time-consuming and followed a learning curve. We also believe that the ability to store clinical images into patients' medical records (with patient consent) would be beneficial; by

Table 1. Type of data in referrals composed of clinical information and clinical images

Type of data	Adequate clinical Images	Inadequate clinical images
Adequate clinical information	96 (29%)	32 (9.7%)
Inadequate clinical information	119 (35.9%)	84 (25.4%)

Table 2. Type of data in referrals composed of clinical information or clinical images

Type of data	Adequate	Inadequate
Clinical information	9 (30%)	21 (70%)
Clinical images	81 (73.64%)	29 (26.36%)

Table 3. Time of response by a dermatologist after referral

Time of response	All referrals	Inpatient referrals	Outpatient referrals
Less than 24 h	419 (88.9%)	138 (97.2%)	281 (85.4%)
24-48 h	7 (1.5%)	0	7 (2.1%)
48-72 h	30 (6.4%)	0	30 (9.1%)
More than 72 h	15 (3.2%)	4 (2.8%)	11 (3.3%)

Table 4. Conversion to in-person evaluation and average time for consultation

Conversion to in-person evaluation	Conversion to in-person evaluation	Average time to in-personal evaluation
All referrals	273 (58%)	–
Inpatient referrals	43 (30.3%)	0.25 days
Outpatient referrals	230 (69.9%)	4 days

doing this, important clinical data would be made available to all physicians involved in a given patient's care, regardless of medical specialty. Current storage options available at CHULC don't grant access to this data to non-dermatologists and make future erasing of said data (due to low storage capacity, change of e-mail domains, among others) an inevitability.

Nevertheless, the successful implementation of teledermatology methods is directly impacted by the quality of the sent data. In an ideal world, only adequate clinical information and clinical pictures would be received. In this study, this was true in less than a third of referrals containing both types of data.

Without clear and detailed clinical information, the interpretation of the patient's condition becomes difficult, making diagnosis and treatment a challenge; frequently, past medical history of patients was omitted in referrals and the evolution of the dermatosis through time was not always described. Likewise, description of past medical treatments was missing most of the time.

The absence of a clear description of dermatologic lesions was frequently found in referrals. Incorrect use of medical terms regarding primary and secondary skin lesions (especially when clinical images are lacking or inadequate), can misguide diagnosis. This problem can be addressed with adequate education of non-dermatologists regarding standard definitions of dermatological terms.

On the other hand, clinical pictures without good quality also undermine these clinical processes. Lack of focus and insufficient lighting were the most common problems identified and can be, at least partially, justified by lack of specific formation in clinical image of adequate cameras owned by the hospitals and the need to use personal cameras or taking, lack of ideal physical conditions (natural lighting for example) and time to produce adequate clinical images. Absence of adequate cameras owned by the hospitals and the need to use personal cameras or smartphones can also impact image quality.

Other difficulties arise when considering the almost 30% of cases in which referrals were only composed of clinical information or clinical pictures. This is unsatisfactory for all the previously mentioned reasons, adding up to the need of subsequent follow-ups on referrals (which increases workload not only for the dermatologist but also for the physician responsible for the referral). If this process, albeit cumbersome, can be made in inpatients referrals, its application to outpatient referrals was sometimes impossible (i.e., obtaining clinical pictures of a patient that had already left the emergency room). Evidently, one must also consider that all of this is directly reflected in delaying patient care.

It is also noteworthy the acceptance of teledermatology by patients. All patients in which the use of these methods was suggested by their physician gave their informed consent. High acceptance of COVID-19 control measures (including mobility restrictions) among Portuguese population, desire to avoid more in-person consultations and the prospect of a faster clinical response were probable drivers for this fact.

Accordingly, clinical response by a dermatologist was produced in less than 24 hours in almost 90% of all

referrals, approaching almost 100% in inpatient referrals. Longer response times were associated with referrals made during the weekend or holidays (as the dermatology department only functions during working days).

Conversion to in-person evaluation was made when the clinical information and/or images were insufficient to arrive at a diagnosis, when medical or surgical procedures were necessary (as in malignant tumors) and when the complexity of the medical condition demanded it (erythrodermic patients, among others). We also consider that the average time for in-person evaluation was satisfactory.

The striking difference in conversion to in-person evaluation between inpatient and outpatient referrals can be justified, in part, by the nature of the referrals themselves. In the first case, most patients didn't present with dermatological urgencies and were referred mostly for benign, long-term and easy to treat conditions, thus taking advantage of a hospitalization for other medical reasons for this dermatological evaluation. In contrast, a significant portion of outpatient referrals consisted of urgent or complex conditions that demanded in-person evolution, and that, in most situations, had driven the patient to an emergency room consultation in the first place.

Our study has several limitations: deleted or lost data at the time of the study couldn't be included in this analysis and, even with pre-established criteria, the classification of "adequat". and "inadequat". clinical images is always observant-dependent at some level.

Arguably, the pandemic accelerated the process of implementation of new technologies to deliver better healthcare and so, even after the restrictions imposed by COVID-19 were lifted, the Dermatovenereology Department of HSAC maintained its teledermatology platforms. By allowing clinical triage and remote consultations for clinical situations where in-person evaluation is not mandatory, teledermatology made possible a faster delivery of care, while lowering work absenteeism and costs for patients and health providers.

Conclusion

The COVID-19 pandemic gave rise to a number of difficult to overcome challenges. In this particular case, the need to balance assistential activity and COVID imposed restrictions was met with the implementation and use of teledermatology methods. These were widely and rapidly accepted by physicians and patients.

During a 13-month period, the Dermatology and Venerology Department of HSAC received more than 500 referrals for inpatient and outpatient consultations, composed of clinical information and/or clinical images. A significant proportion of these was resolved remotely without the need for in-person consultation.

Insufficient clinical information in referrals, inadequate clinical images and lack of integration with clinical software were the main problems identified by this study. Its resolutions aren't straightforward and would involve education of professionals and financial support in order to acquire new equipment and software.

Telemedicine cannot, by any means, fully replace in-person evaluation of patients and presents itself with a particular array of problems. Nevertheless, it can be a valuable work tool for professionals, especially in atypical times when all available resources must be used to assure good healthcare.

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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ORIGINAL ARTICLE

Laboratory diagnosis and prevalence of onychomycosis caused by *Fusarium* and *Scytalidium* species

Diagnóstico laboratorial e prevalência de onicomicose causada por espécies de *Fusarium* e *Scytalidiu*

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Abstract

Introduction: *Scytalidium* and *Fusarium* are opportunistic saprophytic fungi commonly found in subtropical areas, being responsible for several cases of onychomycoses caused by non-dermatophytic filamentous fungi in these regions. The aim of this study is to determine the prevalence of onychomycoses caused by these pathogens, which population and site of infection are most affected, and which morphological characteristics should be considered for the culture method. **Methods:** A 5-year retrospective analysis was performed with data collected from mycological examinations at a clinical analysis laboratory located in Porto Alegre, Rio Grande do Sul, Brazil. **Results:** Of the 2479 cases of onychomycosis studied, *Scytalidium* and *Fusarium* had a prevalence of 3% and 7%, respectively. About 57% of these infections affected women aged 30-69 years. In 78% of the cases of onychomycosis, toenails were affected. Positive reports of *Scytalidium* spp. exhibited chain-shaped arthroconidia, while *Fusarium* spp., fusiform, elongated or canoe-shaped macroconidia, and elongated ovoid microconidia were observed. **Conclusion:** This retrospective study revealed that *Fusarium* spp. has a higher prevalence than *Scytalidium* spp. The feet are the most affected body region. Elderly women are the most affected population by these fungi. For diagnosis, the main findings of *Scytalidium* spp. and *Fusarium* spp. are the cylindrical chain arthroconidia and the canoe-shaped, fusiform, or half-moon-shaped macroconidia, respectively.

***Keywords*:** Onychomycosis. *Scytalidium. Fusarium.*

RESUMO

Introdução: Os fungos *Scytalidium* e *Fusarium* são sapróbios oportunistas que tem como habitat regiões subtropicais, sendo responsáveis por *grande* parte das onicomicoses causadas por Fungos Filamentosos não Dermatófitos nestas regiões. O objetivo deste trabalho foi determinar a prevalência das onicomicoses causadas por esses fungos, a região mais afetada, grupo populacional mais acometido e quais características morfológicas devem ser consideradas utilizando o método cultural. **Métodos:** Foi realizada uma análise retrospectiva de dados dos últimos cinco anos, utilizando laudos de exames micológicos de um laboratório de análises clínicas localizado na região de Porto Alegre. **Resultados:** Foi identificado uma prevalência

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de 3% para o *Scytalidium* spp. e 7% para o *Fusarium* spp., onde 57% das infecções acometeram mulheres com idade entre 30-69 anos e em 78% as unhas dos pés foram afetadas. Os laudos positivos para *Scytalidium* spp. apresentaram artroconídios em cadeia, já para o *Fusarium* spp. foram observados macroconídios fusiformes, alongados ou em canoa e microconídios *ovoides* e alongados. **Conclusão:** Esta análise revelou que o *Fusarium* spp. tem *maior* prevalência que o *Scytalidium* spp., sendo a região dos pés a mais acometida, e as mulheres em idade adulta as mais afetadas por estes fungos. Para o diagnóstico, os principais achados dos fungos *Scytalidium* spp. e *Fusarium* spp., são os artroconídios cilíndricos em cadeia e os macroconídios em formato de canoa, *fusiforme* ou meia-lua, respectivamente.

***Palavras-chave*:** Onicomicose. *Scytalidium*. *Fusarium*.

Introduction

Over recent years, the number of cases of onychomycosis caused by non-dermatophytic filamentous fungi (NDF) has increased, with a high prevalence of *Scytalidium* and *Fusarium* species[1-3]. As well as dermatophytes, *Scytalidium* and *Fusarium* are keratinase-producing fungi and, due to this ability, they become primary nail pathogens–unlike other NDF that do not have this ability and, therefore, are often considered secondary pathogens or contaminants[4-6].

Scytalidium is considered an endemic pathogen in hot-humid climate areas. The most known species to cause onychomycosis are *S. dimidiatum* and *S. hyalinum*. Both are filamentous fungi identified by the branching, septate hyphae with arthroconidia arranged in the chain and aerial mycelium of grayish to black color, which differentiate them from dematiaceous and hyaline fungi, respectively[1,4,7].

Fusarium is a hialohyphomycete with *optimum* temperature growth between 25 and 30°C. Micromorphological characteristics of this fungi reveal canoe-shaped septate macroconidia and the aspect of the colony shows a felty mycelium with different colors[8,10]. The main species that cause onychomycosis are *F. solani* and *F. oxysporum* and they can be differentiated by their micromorphological features[4,8,9]. *F. solani* microconidia are larger, more oval, and have a thicker wall, however, it is difficult to make this distinction only through microscopy examination[10].

For the correct microbial identification of these pathogens, it is essential to carry out a culture test. The direct examination does not allow mycologic identification, since the reproductive structures can only be identified within the culture by the micromorphological aspects[11]. Besides the difficulties of fungal identification, these species have an increased resistance to the available antifungal drugs for dermatological use[8].

Onychomycosis caused by NDF has predisposing factors that include tropical and subtropical climate, mechanical trauma, prolonged use of closed shoes, hyperhidrosis, family history, and immunosuppression, mainly in HIV patients[2,5]. In most cases, NDF causes superficial infections, however, immunocompromised patients can develop a systemic disease[5,7,8]. Within this framework, the correct diagnosis carried out with direct examination, culture test and fungal antibiogram are crucial to an effective therapy–avoiding antifungal resistance and toxic effects[5].

The aim of this study is to demonstrate the main features of the structures of *Fusarium* spp. and *Scytalidium* spp. important for a reliable mycological diagnosis. Using data obtained from the mycology sector of a clinical analysis laboratory located in Porto Alegre, Rio Grande do Sul, Brazil, epidemiologic aspects, such as prevalence, age, and sex of the patients were evaluated.

Methods

Data collected from the mycological examination obtained from a clinical analysis laboratory located in Porto Alegre/RS was evaluated through a transversal retrospective 5-year analysis from January 2017 to December 2021. The frequency of fungi diagnosed by mycological culture was analyzed and divided into two samples: onychomycosis caused by *Scytalidium* spp. and onychomycosis caused by *Fusarium* spp. Each sample was subdivided into macro- and micromorphology, and the age and sex of the patients, site of infection, and year of the examination were also collected.

The prevalence of *Fusarium* spp and *Scytalidium spp* infection was determined using all culture methods available in the clinical analysis laboratory, with or without direct examination, dividing the laboratory test reports into onychomycosis and another dermatomycosis (such as skin or scalp lesions, and secretions). Exclusion criteria were (i) laboratory test reports that revealed fungal contamination; and (ii) direct examinations that detected *Malassezia* spp. since the correct

Table 1. Results of culture tests performed for the diagnosis of onychomycosis in the last 5 years

	Year					
Diagnosis	**2017**	**2018**	**2019**	**2020**	**2021**	**Total (%)**
Dermatophytes	139	161	148	255	178	881 (35.5)
Yeasts	65	144	91	24	21	345 (13.9)
NDF	81	100	93	48	47	**369 (14.9)**
Negatives	100	166	226	120	272	**884 (35.7)**
Total	**385**	**571**	**558**	**447**	**518**	**2479 (100)**

NDF: non-dermatophytic filamentous fungi; **(%)** percentage calculated in relation to the number of culture tests performed for onychomycosis (2479).

identification of this fungi requires a positive culture in a specific growth medium[11,12].

The nail samples were collected using sterile pliers and sent to the mycology sector of the laboratory, followed by direct examination and culture tests. For the direct examination, part of the sample was processed with potassium hydroxide 20% for clearing the specimens and enhancing the microscopic observation of fungal structures. For fungal identification, fungal culture tests were used. The samples were inoculated in Potato Dextrose Agar and Sabouraud Dextrose Agar with Chloramphenicol and incubated for a period of 21 days at 25°C.

Results

During the study period, 7250 mycological examinations (direct examination and/or fungal culture test) were performed. Out of the 7250 laboratory test reports, 3426 fungal culture tests were solicited for diagnosis of cutaneous lesions, 2479 for onychomycosis, and 839 for other dermatomycoses. A total of 1595 cases of onychomycosis and 383 other dermatomycoses were confirmed. Among the 1595 confirmed cases of onychomycosis, 881 (55.24%) were positive for dermatophytes, 345 (21.63%) for yeasts, and 369 (23.13%) for NDF. As seen in Table 1, prevalence rates for dermatophytes were 35.5%, 13.9% for yeasts, and 14.9% for the NDF.

Among all samples identifying NDF group, 280 laboratory test reports were positive for *Scytalidium* spp. and *Fusarium* spp., 249 in cases of onychomycosis, representing about 10% of the analyzed samples from onychomycosis (2479). Out of 249, 175 (7%) confirmed *Fusarium* spp. and 74 (3%) *Scytalidium* spp. A relevant feature was the negative direct examination in 199 of the 249 samples, representing 79.9% of the total. Table 1 shows the distribution of findings for each year.

Onychomycosis cases caused by most NDF decreased in the last years–exhibiting their highest number in 2018. However, *Fusarium* spp. showed a gradual increase, with 40 cases in the year 2020, when it reached its peak representing 83% of the onychomycosis caused by NDF. In 2021, *Fusarium* spp. reports decreased. For *Scytalidium* spp., the incidence of the pathogen has decreased by more than 50% since the study was started (Table 2). Concerning another dermatomycosis, NDF was found in 31 cases, eight cases in 2017 and 2018, six cases in 2019, three in 2020, and six in 2021.

Among the 74 cases of onychomycoses caused by *Scytalidium* spp., 63.5% were females and the most affected age group was between 30 and 39 years (17.6%), whereas for the 175 cases caused by *Fusarium* spp., the most affected group were women (74.9%) aged between 50 and 59 years (18.9%) (Table 3).

The site of the affected nail was also evaluated. For *Scytalidium* spp., 79.8% of the cases affected the toenails, 2.7% the fingernails, and 1.3% both were infected and 13.5% of the samples were related to another dermatomycosis. For *Fusarium* spp., toenails also represented 78.3% of the cases, and fingernails 9.1%. Both fingernails and toenails were infected by *Fusarium* spp. in 2.3% of the cases and 6.9% of the samples were collected from other dermatomycoses. As seen in Table 4, the prevalence of affected toenails is significantly higher compared to other sites of infection for both pathogens.

In 12 cases (4.8%) these NDF fungi were considered contaminants since there was a coinfection by dermatophytes.

Morphological characteristics of *Fusarium* spp. include clear surface colonies with variations in reverse (white,

Table 2. Number of positive mycological tests for *Scytalidium* spp. and *Fusarium* spp. in onychomycosis from January 2017 to December 2021

	Year					
	2017	**2018**	**2019**	**2020**	**2021**	**Total**
Scytalidium spp.	25	19	16	7	7	74
Fusarium spp.	37	33	38	40	27	175
Total (%)	62 **(24.9)**	52 **(20.9)**	54 **(21.7)**	47 **(18.9)**	34 **(13.6)**	249

(%) Percentage of the total number of positive reports of onychomycosis caused by *Scytalidium* spp. and *Fusarium* spp. among the 249 cases by NDF.

Table 3. A number of cases of onychomycosis by *Scytalidium* spp. and *Fusarium* spp. separated by sex and age of the patients

	***Scytalidium* spp. (Total = 74)**		***Fusarium* spp. (Total = 175)**	
Age	**Women (%)**	**Men (%)**	**Women (%)**	**Men (%)**
0-9	0 (0)	0 (0)	1 (0.6)	0 (0)
10-19	0 (0)	0 (0)	2 (1.1)	1 (0.6)
20-29	0 (0)	6 (8.1)	16 (9.1)	6 (3.4)
30-39	13 (17.6)	9 (12.2)	22 (12.6)	11 (6.3)
40-49	8 (10.8)	6 (8.1)	27 (15.4)	10 (5.7)
50-59	8 (10.8)	5 (6.8)	33 (18.9)	7 (4)
60-69	12 (16.2)	1 (1.3)	18 (10.3)	5 (2.9)
70-79	3 (4.05)	0 (0)	5 (2.9)	3 (1.7)
80-89	3 (4.05)	0 (0)	7 (4)	1 (0.6)
Total (%)	47 **(63.5)**	27 **(36.5)**	131 **(74.9)**	44 **(25.1)**

(%) Percentage refers to the number of positive reports of onychomycosis caused by *Scytalidium* spp. (74) and *Fusarium* spp. (175).

Table 4. Comparison between the numbers of cases relating to the characteristics found in the mycological reports

	Samples of *Scytalidium* spp. (74) n (%)	**Samples of *Fusarium* spp. (175) n (%)**	**Total samples (249) n (%)**
Positive direct examination	18 (24.3)	31 (17.7)	49 (19.7)
Negative direct examination	56 (75.7)	143 (81.7)	199 (79.9)
Direct examination not performed	0 (0)	1 (0.6)	1 (0.4)
Dermatophyte-associated	6 (8.1)	6 (3.4)	12 (4.8)
Site of infection			
Hallux	17 (23)	35 (20)	51 (20.5)
Affected hallux (right or left)	17 (23)	61(34.9)	78 (31.3)
Thumbs	0 (0)	2 (1.1)	2 (0.8)
Toes	25 (33.8)	41 (23.4)	66 (26.5)
Fingers	2 (2.7)	14 (8)	16 (6.4)
Fingernails + toenails	1 (1.3)	4 (2.3)	5 (2)
Nail + skin infection	10 (13.5)	12 (6.9)	22 (8.8)
Nails (no site recorded)	3 (4)	6 (3.4)	9 (3.6)

(%) Percentage refers to the number of positive reports of onychomycosis caused by *Scytalidium* spp. (74), *Fusarium* spp. (175) over the total of samples (249).

beige, salmon, pink, violet, orange, red and brown), filamentous, with a cotton-like aspect, as shown in Fig. 1.

Morphological characteristics of *Scytalidium* spp. reveal dark colonies, ranging from brown to black or gray (Fig 2A to C), with the exception of *Scytalidium hyalinum* which may have a white colony (Fig. 2D).

Discussion

Scientific literature indicates that dermatophytes are the most frequent agents of onychomycosis, representing about 80-90% of the cases[4-6]. Furthermore, yeasts account for about 5-17%, while the frequency of NDF

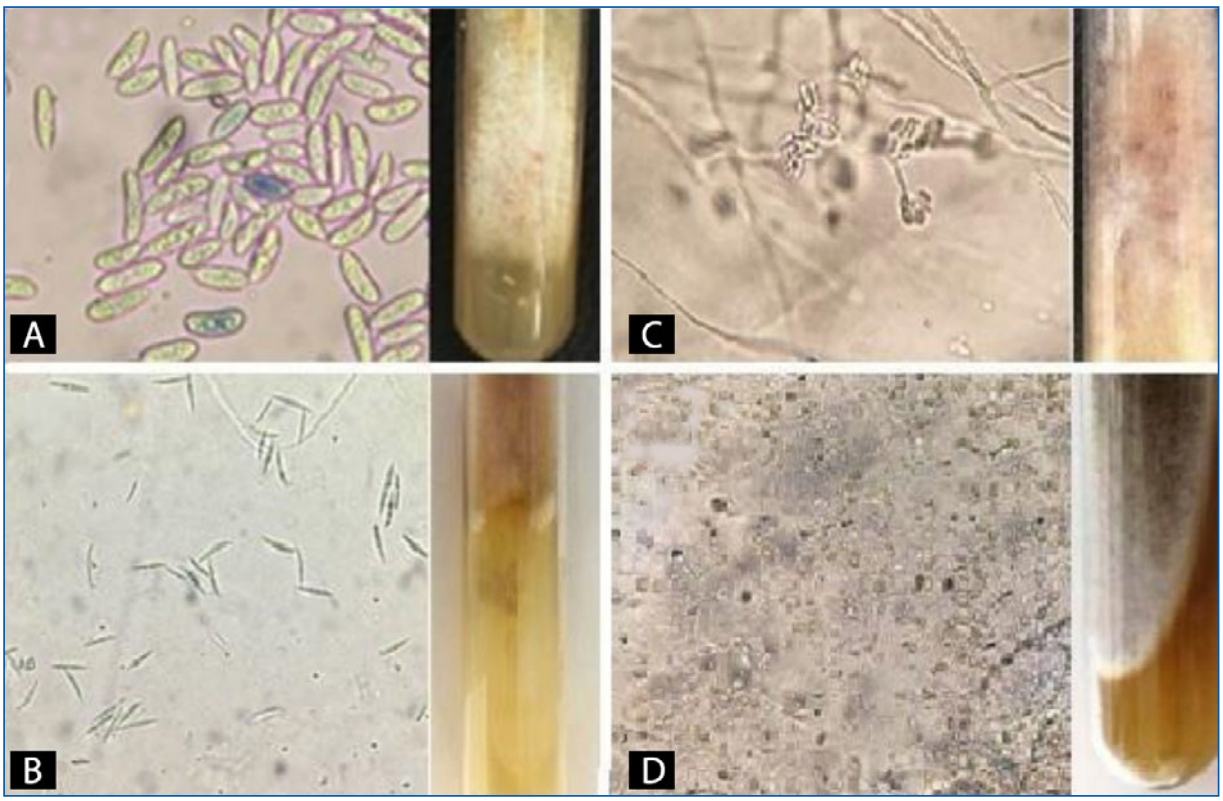

Figure 1. *Fusarium* spp. **A:** elongated and ovoid macroconidia, some microconidia with the same shape as macroconidia, presenting pink refringence and white colony with a white reverse and yellow and pink pigmentations. **B:** fusiform macroconidia and beige colony with brown reverse, filamentous appearance. **C:** microconidia grouped in "false heads" and white colony with salmon reverse. **D:** many oval and pyriform microconidia, some fusiform macroconidia and loose and chained chlamydoconidia, a white colony with dark brown reverse. (Source: Mont' Serrat Laboratory).

varies from 2 to 22%[2,13,14]. In addition to the pathogens of interest in this study, many species belong to the NDF group, such as *Curvularia* spp., *Acremonium* spp., *Scopulariopsis brevicaulis,* and *Aspergillus* spp.[4-6]. In this study, the frequency of NDF and yeasts detected in onychomycosis (respectively 23 and 22%) is increased compared to literature[2,6], whereas dermatophytes were less frequently observed (55%). *Fusarium* spp. and *Scytalidium* spp. represent 11% and 4.63%, respectively.

A study in Rio de Janeiro, Brazil, showed that 11.86% of onychomycosis was caused by NDF. Besides, Cursi et al.[3] found that 4.86% of the nail infections were caused by *Scytalidium* spp., representing 40.9% of NDF group. Females were the most affected (2:1) and were aged between 40 and 60 years. On the other hand, our study revealed that despite the similar prevalence (3%), the sample (74) represented 20% of the NDF, also having a predominance of females (2:1). However, the age group was younger (30-39 years). Both studies demonstrate that NDF nail infection is not a rare situation[3].

A recent study[2], also performed with *Fusarium* spp. and *Scytalidium* spp., exhibited a high prevalence of these pathogens in adult women. The authors correlated *Fusarium* spp. infection, with pedicure history, as women often go for pedicures and also with their tendency to have more contact with the ground, since they wear open shoes more often. These may be explanations for such findings, as we also found in the sample (175) a prevalence of women (3:1) aged 50-59 years. Moreover, elderly people tend to have a higher incidence of onychomycosis because they have less nail growth and more circulation problems that disrupt nail plate morphology and also have more frequent underlying diseases[2].

Onychomycosis represents up to 50% of nail diseases[15] and can be classified according to their location and mode of invasion. The most common forms are distal lateral subungual onychomycosis (DLSO), proximal subungual onychomycosis, superficial onychomycosis, and total dystrophic onychomycosis[5,6]. The manifestation of DLSO, which predominates in the feet, is the most common form of involvement by *Scytalidium* and *Fusarium*. This infection caused by these NDF is indistinguishable from DLSO caused by dermatophyte fungi.

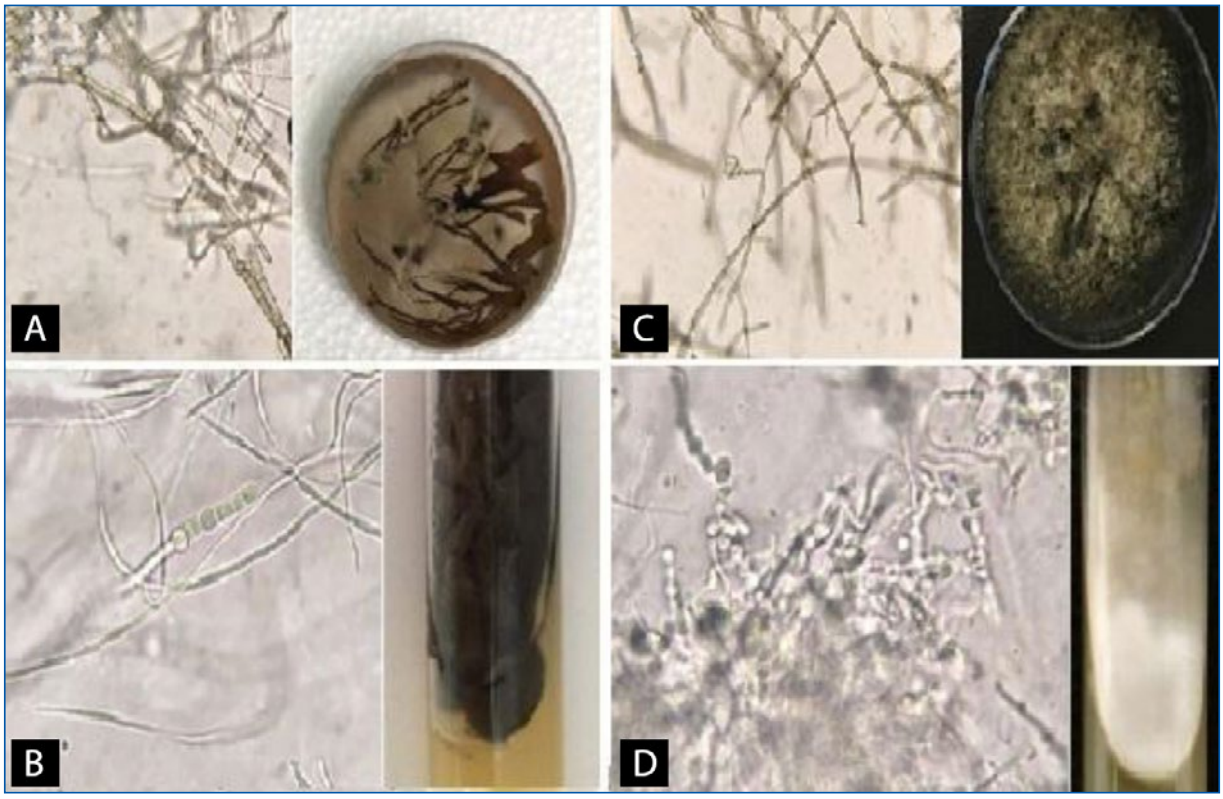

Figure 2. *Scytalidium* spp. **A:** broad demaceous and septate hyphae, some thin and hyaline hyphae, arthroconidia in the chain of oblong shape, and grayish-brown colony with dark-brown reverse, characteristic of *Scytalidium dimidiatum*. **B:** two types of hyphae, dematiaceous and hyaline, chain of plump arthroconidia generated from the hypha and black colony with yellow reverse. **C:** long chains of cylindrical arthroconidia with or without septum and gray colony with black reverse. **D:** arthroconidia in round chains and hyaline hyphae, a white colony with yellowish reverse, characteristic of the species *Scytalidium hyalinum*. (Source: Mont' Serrat Laboratory).

Gupta et al.[16] reviews is frequently used as a reference for the diagnosis of onychomycosis caused by NDF. They point out that it is necessary to meet at least three of the following features to be considered a true positive result: identification by direct examination, isolation of NDF in fungal culture, repeated isolation in culture, exclusion of dermatophytes, inoculum counting, and histopathology[2-4,16].

NDF found in samples collected for the diagnosis of onychomycosis could indicate primary pathogens, contaminants, transient colonization, secondary colonizers, and persistent secondary colonizers. This implies that the nail can be initially infected by a dermatophyte and then by a NDF, even after antifungal therapy–which often generates selective pressure causing resistant fungi to continue colonizing the nail[5]. Therefore, the association with dermatophytes found in 4.8% of the cases in this study does not necessarily mean contamination and exclusion of the pathogenic effect of the NDF, which may be classified as a secondary pathogen.

Many studies[2,3,5,15,16] prioritize fungal identification during the direct microscopic examination. However, it is known that several factors interfere with the result, such as previous use of antifungal drugs, the technical skill of the operator, and mainly preanalytical questions such as poor hygiene prior to sample collection, poor investigation of the use of antifungal drugs and inadequate sample collection in addition to the fact that the procedure must be performed in a manner compatible with the type of pathology[6,11]. Quatrin et al.[11] in a comparative study revealed that the positive predictive values and negative predictive values of direct mycological examination are 78% and 44%, respectively, compared to a fungal culture which is 97% and 91%, reinforcing the importance of performing mycological cultures in all cases. Actually, in the present study, about 80% of the samples with a positive culture were negative on the direct microscopic examination.

As mentioned above, one of the criteria for validating the diagnosis of onychomycosis caused by NDF is repeated isolation in fungal culture. However, there is

great difficulty in getting patients to return for repeat exams, both for logistical and financial reasons. Therefore, it is difficult to apply this method in clinical laboratories. The inoculum counting is also considered one of the criteria, however, for *Scytalidium* and *Fusarium*, filamentous fungi that form a "carpet" over the entire plate as shown in Figure 1 and 2, it is not possible to perform this counting. Still, on the validation parameters, histopathology can also be used for evaluation, and despite supplying the deficiencies of the direct examination, it requires more steps in the preparation of the slide and a pathologist to analyze[5,15] which is not part of the routine of the clinical analysis laboratory of this study.

Furthermore, it is important to consider that *Fusarium* and *Scytalidium* are mainly parasites of vegetation, being facultative parasites of humans. Mimicking the ideal environment for the growth of these fungi is extremely difficult. In this way, attention should be paid to the structures that grow in the cultural media, especially in cases of cultural examinations with the growth of a single microorganism considering that contamination usually occurs by the growth of more than one fungal type in the same culture.

Regarding the microscopic and macroscopic structural features of *Fusarium* spp., most samples revealed hyaline hyphae and microconidia in different shapes–oval, ellipsoid, piriform, and fusiform, loosely arranged or grouped together in "false heads" (Fig. 1C). In this case, operator experience is crucial, as it can be confused with *Acremonium* spp., which forms clusters of fusiform microconidia. Chlamydoconidia, structures typical of fungal resistance[17], were also visualized (Fig. 1D). The color of the mycelium ranged from white to beige, with the reverse of different colors (pink, violet, orange, brown and red). For a correct diagnosis, it is necessary that macroconidia are visualized since they are specific to each species. *Fusarium* spp. macroconidia are larger structures than their microconidia and have the shape of a banana, a canoe, or a half-moon (Fig. 1).

On the other hand, *Scytalidium* spp. showed two hyphae shapes. One type has hyaline, smooth, and narrow hyphae and the other has wide, dematiaceous, and septate hyphae, as shown in Fig. 2. The main feature is the arthroconidia long rows, formed from the hyphae. These arthroconidia have a plump or cylindrical shape and the mycelium has a flaky texture. Some colonies are dark (black, gray or brown) with a yellow to dark brown reverse and others are white colonies with a yellow reverse (Fig. 2).

During the analysis of the data (Table 1), it was noticed that in 2020 and 2021 there was a sudden decrease in positive reports for NDF and despite the number of mycological cultural tests performed in the period was slightly lower than in 2018 and 2019, this large drop in cases is not well clarified. However, these years coincide with the period of the SARS-CoV-2 coronavirus pandemic, and hygiene and health care guidelines were strongly recommended, which may have led to a decrease in cases of these environmental and opportunistic fungi and explain the reduction of positive reports for *Scytalidium* and *Fusarium*.

Conclusion

Onychomycosis caused by NDF is a significant problem even though it decreased in the last 5 years, due to a decrease in the cases due to *Scytalidium* spp. However, *Fusarium* spp. reports remain high compared to the overall picture. Adult women are the most affected group and the feet are the most affected site of infection for both pathogens. For the diagnosis, it is essential to perform the fungal culture. For correct identification, technical skills and scientific knowledge are crucial to identify the particular characteristics of *Fusarium* spp. (fusiform micro and macroconidia) and *Scytalidium* spp. (oblong-shaped chain arthroconidia).

Conflict of interest

No conflict of interest declared.

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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ORIGINAL ARTICLE

Isotretinoin treatment and risk of depression in acne vulgar patient: what is the evidence?

O tratamento com isotretinoína e o risco de depressão em doentes com acne vulgar: qual a evidência?

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Abstract

Introduction: Acne vulgaris is a chronic inflammatory skin disease that often affects teenagers and young adults. The approach and treatment depend on the location, morphology, and severity of acne. Oral isotretinoin, used in the treatment of severe or refractory nodular acne, may be related to the development of psychiatric pathologies, such as depression or suicidal ideation. The aim of this review is to determine whether isotretinoin treatment is associated with the development of depression in patients with acne vulgaris. **Methods:** A systematic review of scientific evidence published in electronic databases, using the MeSH terms *isotretinoin*, *acne,* and *depression*. The Strength of Recommendation Taxonomy Scale was used to assess the studies' quality and the recommendation's strength. **Results:** A total of 142 articles were identified and five met the inclusion criteria: two meta-analyses and three cohort studies (two prospective and one retrospective study). **Discussion:** The risk of depression associated with taking isotretinoin by acne patients has been a concern and a controversial topic, however, the results are consensual in stating that there doesn't seem to exist any evidence of this association. It was also found that acne treatment, regardless of drug, seems to improve depressive symptoms. The heterogeneity of the studies, the small sample size, and the absence of randomized clinical trials are some limitations. More studies are needed to confirm these findings.

***Keywords*:** Isotretinoin. Acne. Depression.

Resumo

Introdução: A acne vulgar é a doença inflamatória crónica da pele, que afeta frequentemente adolescentes e adultos jovens. A abordagem e tratamento dependem da localização, morfologia e gravidade da acne. A isotretinoína oral, utilizada no tratamento da acne nodular grave ou refratário, pode estar relacionada com o desenvolvimento de patologia psiquiátrica, como depressão ou ideação suicida. Com esta revisão pretende-se determinar se o tratamento com isotretinoína está associado ao desenvolvimento de depressão em doentes com acne vulgar. **Métodos:** Revisão sistemática da evidência científica publicada em bases de dados eletrónicas, utilizando os termos MeSH *isotretinoin*, *acne, depression*. Foi utilizada a escala *Strength of Recommendation Taxonomy* para avaliar a qualidade dos estudos e força de recomendação. **Resultados:** Foram identificados 142 artigos, dos quais cinco cumpriram os critérios de inclusão: duas metanálises e três estudos de coorte (dois

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prospetivos e um retrospetivo). **Discussão:** O risco de depressão associado à toma de isotretinoína por doentes com acne tem sido uma preocupação e um tema controverso, no entanto os resultados desta revisão são consensuais a afirmar que não parece existir evidência sobre essa associação. Verificou-se ainda que o tratamento daacne, independentemente do fármaco, parece melhorar os sintomas depressivos. A heterogeneidade dos estudos, o pequeno tamanho amostral e a ausência de ensaios clínicos aleatorizados são algumas das limitações. Mais estudos são necessários para confirmar estes achados.

***Palavras-chave*:** Isotretinoína. Acne. Depressão.

Introduction

Acne vulgaris is a chronic inflammatory skin disease that often affects adolescents and young adults[1]. It originates in the pilosebaceous follicle and is characterized by increased sebum production, follicular hyperkeratinization, inflammation, and bacterial proliferation of *propionibacterium* (*P. acnes*)[2]. There are several predisposing factors that have been considered, from environmental to hormonal, dietary, and genetic factors[1]. Clinically it is manifested by noninflammatory (open and closed comedones), inflammatory (papules, pustules, nodules, and cysts) and residual lesions (scars, hyperpigmented macules), which appear on the face, chest, and upper part of the trunk[2,3]. Scars and keloids can affect the quality of life and be associated with depression, anxiety, and suicidal ideation[1,3].

The approach and treatment depend on the location, morphology, and severity of acne[2]. Isotretinoin is a first-generation retinoid (vitamin A derivative) that acts directly on the pilosebaceous follicle, with decreased sebum production and a comedolytic effect.[2] Oral isotretinoin is used in the treatment of severe or refractory nodular acne[2,4]. The most frequent side effects are xerosis, xerophthalmia, cheilitis, headache, dyslipidemia, and increased hepatic transaminases[2,4]. Psychiatric pathology, such as depression and suicidal ideation, may be related to the use of isotretinoin, however, this association is not yet clarified[2,4].

In this sense, it was considered relevant to review the existing scientific evidence on the association between isotretinoin and the risk of depression in patients with acne.

Methods

A nonquantitative systematic search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations[5]. Clinical guidelines, systematic reviews, and original studies were searched in Pubmed, Cochrane Library, Embase, Scopus, National Institute for Health and Care Excellence Guidelines Finder, National Guideline Clearinghouse, Canadian Medical Association Practice Guidelines InfoBase, Database of Abstracts of Reviews of Effectiveness (DARE), Bandolier, British Medical Journal Clinical Evidence, Evidence-Based Medicine Online, published between January 2017 and January 2022. The MeSH terms isotretinoin, acne, and depression were used. The PICO model was used to formulate the research question: (i) Population: patients with acne vulgaris; (ii) Intervention: treatment of acne with isotretinoin; (iii) Comparison: other acne treatments; (iv) Outcome: risk of depression in acne patients under treatment with isotretinoin. Studies in Portuguese, English, or Spanish, with full text and carried out in humans, were included. The following exclusion criteria were considered: duplicate articles, opinion articles, classic review articles, clinical cases, and articles in disagreement with the objective of the review.

The selection of articles was made in duplicate by the first and third authors who, in case of doubt, would discuss the inclusion/exclusion of the article with the second author. The agreement rate between authors in the selection of articles was 100%. All authors performed the full reading and assessed the quality and level of evidence (EL) of the selected articles and the strength of recommendation according to the American Family Physician's Strength of Recommendation Taxonomy (SORT) scale[9].

Results

A total of 142 articles were obtained, of which only five met the inclusion criteria and did not present exclusion criteria: two meta-analyses and three cohort studies, two prospective and one retrospective. The article selection phases are demonstrated in Figure 1.

The systematic review and meta-analysis by Li et al.[3], carried out in China, investigated the association between the use of isotretinoin and the risk of depression in patients with acne. A search was carried out in

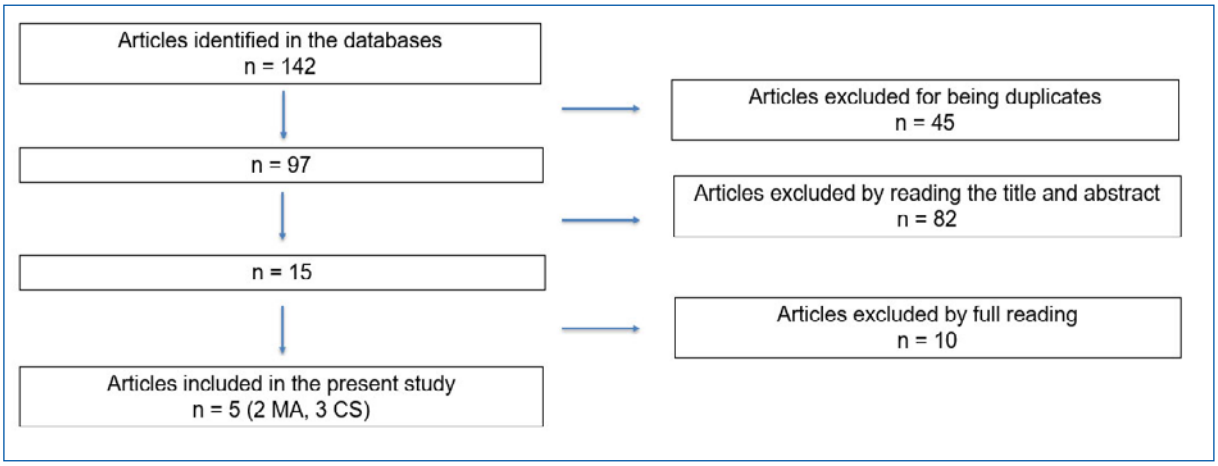

Figure 1. Article selection flowchart.

PubMed, Cochrane Library, and Embase databases, and 20 studies were selected. The study suggested that while isotretinoin could theoretically cause depressive disorders, the risk of depression could be outweighed by its favorable outcome in acne patients. Acne negatively affects the quality of life and self-esteem and can have a significant psychological impact and lead to psychiatric illnesses such as depression. In such matters, isotretinoin can improve the depressive symptoms caused by acne through the improvement or resolution of the associated lesions. The lack of randomized clinical trials, the heterogeneity of the studies (namely in dose and duration of treatment and depression scores), and some of the studies with a small sample size are important limitations of this study.

The most recent study included in this review was carried out in Taiwan by Che et al.[4]. This is a retrospective cohort study following for 16 years 29943 patients with acne, of which 9981 received treatment with isotretinoin and 19962 constituted the control group. Patients with a history of psychiatric illness, aged less than 20 years, and treated with isotretinoin for less than 1 month were excluded. There was no increased risk of psychiatric illness in patients treated with isotretinoin, even with higher dosages or longer duration of treatment. The retrospective character is a limitation of this study.

The systematic review and meta-analysis by Huang et al.[6], carried out in Thailand, evaluated the relationship between the treatment of acne with isotretinoin and the risk of depression. A bibliographic search was carried out in the Pubmed and Cochrane Library databases, and 31 studies were selected that indicated the prevalence of depression or that used depression scales. They concluded that acne treatment with isotretinoin is not associated with an increased risk of depression and that acne treatment appears to improve depressive symptoms. This review's limitations were the great variability of the included studies (for example, regarding the assessment instruments used) and the fact that there was no randomized clinical trial.

Alghofaili et al.[7] performed a prospective cohort study in Saudi Arabia, which included 179 patients of whom 119 were treated with oral isotretinoin, at a daily dose of 0.5 mg/kg, and 60 with different topical treatments (tretinoin or tazarotene). The Beck depression inventory scale was applied before 3 and 6 months after the start of treatment. It was concluded that there is no correlation between isotretinoin treatment and the development of depression and that acne treatment (regardless of drug) is associated with improvement in depressive symptoms. Nonetheless, the small sample size and study design are limiting factors (non-randomized, non-blinded).

In Saudi Arabia, Algandi et al.[8] performed a prospective questionnaire-based cohort study from November 2019 to March 2020 to assess the risk of depression in acne patients treated with isotretinoin, at a daily dose of 0.5 mg/kg, versus doxycycline in a daily dose of 100 mg (control group). The study included 29 patients with moderate to severe acne aged between 18 and 30. Patients with a personal or family history of psychiatric illness, regular use of antipsychotics or antidepressants, or previous treatment with isotretinoin were excluded. Patient Health Questionnaire 9 (PHQ-9) was administered before and 8 weeks after the start of treatment. Eighteen patients (nine men and nine women) completed the study, of whom 12 received treatment with isotretinoin and six received doxycycline. There was no statistically significant difference between the PHQ-9 scores of the two groups concluding that there

Table 1. Summarized description of selected articles

Authors, year	S	Target population and study design	Results/conclusions	Limitations	EL
Li et al., 2019[3]	MA	20 studies	Isotretinoin improves symptoms of depression in acne patients.	RCT not included; some studies with small samples; heterogeneity of studies.	1
Huang et al., 2017[6]	MA	31 studies	No association between Isotretinoin and depression.	RCT not included; great heterogeneity of studies.	1
Chen et al., 2022[4]	CT	(n = 29943) Retrospective study	No association between Isotretinoin and an increased risk of psychiatric illness, including high doses or prolonged duration.	Study in a specific population (Taiwan); risk of suicidal ideation not assessed.	2
Alghofaili et al., 2021[7]	CT	(n = 179) Retrospective study BDI Scale	Isotretinoin for acne does not appear to be associated with a statistically significant risk of depression. Acne treatment improves depressive symptoms.	Small sample size; non-randomized, open-label study.	2
Algamdi et al., 2020[8]	CT	(n = 29) Prospective study, questionnaire PHQ-9	No direct relationship between isotretinoin and the development of depression.	Small sample size.	2

S: study type; EL: level of evidence; SR: systematic review; MA: meta analysis; CS: cohort study; RCT: randomized clinical trial; PHQ-9:- patient health questionnaire 9; BDI: Beck depression inventory.

is no direct relationship between isotretinoin and the development of depression. The small sample size is one of the limitations of this study.

Table 1 summarizes the characteristics and results of the selected studies.

Discussion

The risk of depression associated with isotretinoin treatment in patients with acne has been a concern and a controversial topic[3,6] which motivated this systematic review.

After a detailed analysis of the included studies, we found that there is no evidence that isotretinoin is associated with depression[3,4,6-8].

Chen et al.[4] carried out a cohort study with a larger sample size and, in addition to depression, studied the risk of other psychiatric illnesses (anxiety, bipolar disorder, mania, personality disorder, schizophrenia, and suicide). They concluded that there is no evidence of an increased risk of depression or other psychiatric illnesses linked to isotretinoin.

Li et al.[3] reported heterogeneity of studies in terms of dosage and duration of isotretinoin treatment and were unable to draw conclusions regarding these variables. On the other hand, Che et al.[4] studied the influence of the dosage and treatment duration and showed that there was no increased risk of depression and other psychiatric diseases regardless of the dosage and duration of isotretinoin treatment. In the remaining studies, these variables were not evaluated.

Although the individual susceptibility to depression during treatment with isotretinoin cannot be ruled out, current evidence suggests that treatment of nodulocystic acne with isotretinoin is safe and does not increase the risk of depression[6]. Nevertheless, Che et al. recommend close surveillance of patients with greater susceptibility[4,6].

The strengths of our review are the comprehensive research in several databases, recent studies (published in the last 5 years), and moderate to high quality (with evidence levels 1 and 2).

On the other hand, there are some limitations: no randomized clinical trials were included; some of the studies have a small sample size and present methodological heterogeneity, namely, depression assessment scales, dosage, duration of treatment with isotretinoin, and history of psychiatric illness. Randomized clinical trials would allow for a stronger EL however not treating patients with severe acne with isotretinoin would raise ethical questions. Prospective studies aimed at patients with a psychiatric history may also be of interest.

This evidence-based review demonstrated that treatment of acne patients with isotretinoin does not appear to be related to the development of depression, with a strength of recommendation of A[3,4,6-8]. We further conclude that treatment of acne, regardless of chosen drug, seems to improve depressive symptoms[3,6,7]. More studies, such as randomized clinical trials or other prospective studies with larger sample sizes, are needed to confirm these findings.

What does the study add?

Depression may be related to the use of isotretinoin, however, this association is not yet clarified. In this sense, reviewing the existing scientific evidence on the association between isotretinoin and the risk of depression in patients with acne was relevant. This systematic review demonstrated that treatment of acne patients with isotretinoin does not appear to be related to the development of depression. We further conclude that treatment of acne, regardless of chosen drug, seems to improve depressive symptoms. More studies, such as randomized clinical trials or other prospective studies with larger sample sizes, are needed to confirm these findings.

Ethical disclosures

Funding: This work has not received any type of financial support from any entity in the public or private domain.

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Ethical considerations: The authors declare that throughout the study the criteria established by the Declaration of Helsinki of the World Medical Association updated in 2013 were met.

Awards and prior presentations: The authors declare that this study was presented at UPDATE Congress in Medicine 2022.

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REVIEW ARTICLE

Intralesional triamcinolone acetonide for alopecia areata: does dilution matter?

Acetonido de triancinolonaintralesional na alopecia areata: a diluição importa?

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Abstract

Alopecia areata (AA) is a chronic, remitting, non-scarring form of alopecia, which can be associated with significant emotional distress. Intralesional corticosteroids, particularly triamcinolone acetonide, remain first-line therapy in adults with limited, patchy alopecia areata. However, the optimal concentration of intralesional corticosteroids has not yet been fully elucidated. In this manuscript, we examine current evidence about this matter to guide clinical decision-making.

Keywords: Triamcinolone acetonide. Concentration. Dilution. Alopecia areata. Hair regrowth.

RESUMO

A alopécia areata (AA) é uma forma crónica e remitente de alopécia não cicatricial, que se pode associar a stress emocional significativo. Os corticosteroides intralesionais, particularmente oacetonido de triancinolona, mantêm-se a terapêutica de primeira linha nos adultos com alopécia areata limitada, em placas. No entanto, a concentração idealdo corticosteroide intralesional ainda não foi devidamenteestabelecida. Neste artigo, analisamos a evidência existente sobre este tema, de forma a orientar a decisão clínica.

Palavras-chave: Acetonido detriancinolona. Concentração. Diluição. Alopécia areata. Repovoamento capilar.

Introduction

Alopecia areata (AA), is a chronic, remitting, non-scarring, presumed autoimmune disease of the hair follicles leading to hair loss. AA has a lifetime prevalence of 1.7% and is frequently associated with significant emotional distress. The presence of well-demarcated, hairless patches with yellow dots and short broken hairs (exclamation mark hairs) around the margins is highly diagnostic[1-4].

The choice of treatment depends on the extent of hair loss, previous treatment responses, and the patient's age. For the treatment of localized AA with less than 50% of scalp involvement in adults, intralesional (IL) corticosteroid injection, oral corticosteroids, topical calcineurin inhibitors, and local immunotherapy

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(diphencyprone, anthralin) are considered the best choice[1,5-7].

Triamcinolone acetonide (TA) remains the first-line IL corticosteroid therapy in adults with limited, patchy AA.

The use of IL corticosteroids for the treatment of AA varies between centers and the dilutions and doses of IL injections differ according to the experience of the physician[1,8]. Typically, 2.5 and 5 mg/mL TA concentrations are recommended for the face (beard, eyebrows) and scalp, respectively[9].

Still, the current literature is mostly limited to case series with small sample sizes and heterogeneous patient populations[3].

Herein, we examine current evidence about the best triamcinolone concentration to guide clinical decision-making.

Intralesional corticosteroids

Intradermal corticosteroid injections have been used for the treatment of alopecia areata for many years. Kalkoff & Macher (1958)[10] were the first to report a series using hydrocortisone. Subsequently, Orentreich et al. (1960) described injections of insoluble forms of prednisolone, hydrocortisone, and fludrocortisone as a practical method to treat AA[11], and Gombiner & Malkinson (1961) reported the use of triamcinolone 10 mg/mL[12].

Porter and Burton (1971) described the benefit of IL injections of 10 mg/mL TA and 5 mg/mL triamcinolone hexacetonide[13,14].

A previous open-label randomized study comparing the efficacy of intralesional triamcinolone acetonide (ITA) (10 mg/mL), topical bethametasone valerate foam, and tacrolimus ointment for the treatment of localized AA showed that hair regrowth within 12 weeks was best achieved in the ITA group[15,16]. A meta analysis of 12 studies reported ILA as the most effective treatment in patients with limited AA and a shorter duration of disease, with a response rate ranging from 60 to 95%[8,17]. These studies confirmed IL corticosteroids as a valuable therapeutic tool in AA.

IL corticosteroid injection seems to affect local cytokine expression leading to a gradual decrease in type 1 and type 2 cytokines and IL-23 in parallel with clinical improvement, suggesting that direct suppression of the local immune response is the main mechanism of action[18].

Despite being less potent than betamethasone dipropionate (BD) (0.6 mg of BD corresponds to 4 mg/dL of TA), the low solubility and consequent slow absorption of TA ensures maximum action and minimal systemic effects, which, along with its relatively low cost, make it the most popular among all available steroids[1,8,19].

Injection technique

Corticosteroid is injected into the dermis, with a 0.5-inch long, 30-gauge insulin injector, or a jet injector[1]. The injection is mostly applied at 4-6 week intervals in amounts of 2-3 cc in each session over a treatment duration ranging from 6 weeks to 6 months[3,16]. An injection of less than 0.1 cc is recommended for each injection point[1]. It is estimated that an injection of 0.05–0.01 cc will produce a tuft of hair growth about 0.5 cm in diameter[2]. One should not exceed a maximum dose of 20 mg per monthly session[9].

Concentrations studied

The efficacy of different IL corticosteroid concentrations has been well documented in multiple studies (Table 1). A higher IL corticosteroid index (IL corticosteroid received/ severity score) was proved to correlate with a better hair growth response[1,20]. Though, the best steroid dilution has not been fully elucidated yet.

The concentration of IL corticosteroids tends to vary from 2.5 to 10 mg/mL in different reports[1,21-23]. Typically, 2.5 and 5 mg/mL triamcinolone acetonide concentrations are recommended for the face (beard, eyebrows) and scalp, respectively[9].

Lower concentrations (2.5-3.3 mg/mL)

Ustuner et al. enrolled in one of the few studies comparing the clinical efficacy and safety of different dilutions of ITA (3.3, 5, and 10 mg/mL) and BD. They observed that the injection of four-fold diluted TA (10 mg/dL) was more effective than the 12-fold diluted solution (3.3 mg/mL)[1].

On the other hand, Chu et al. found the injection of 2.5 mg/mL TA as beneficial as the 5 or 10 mg/mL injection[9]. Moreover, skin atrophy was more frequent with 10 mg/mL TA. Thus, the authors advised injection of 2.5 mg/mL TA for limited, patchy alopecia areata involving less than 50% of the scalp[9].

Another recent study compared the results of ITA 2.5 mg/mL with betamethasone 0.375 mg/mL and betamethasone 1.75 mg/mL, and 0.9% saline.

Table 1. Characteristics of the studies included and treatment results of triamcinolone acetonide in alopecia areata

Authors/ publication year	Study design	Number of patients	ITA concentration	Frequency, number and duration of treatments	Definition of response	Results
Abell and Munro 1972[13]	Prospective cohort	84	5 mg/mL	Weekly/twice weekly; 3 treatments	Not defined	86% regrowth at 6 weeks 62% 12 weeks
Porter and Burton 1971[14]	Prospective cohort	17	10 mg/mL	Single injection	Not defined	64% acceptable hair regrowth
Frentz 1977[25]	CCT	12	5 mg/mL	Every 4 weeks 2-4 treatments	subjective	50%
Narahari 1996[28]	CCT	37	10 mg/mL	Every 2 weeks Up to 2 months	Uniform eruption of hair follicles	84%
Kubeyinje and C'Mathur 1997[37]	Open-label CCT	58	40 mg (nonspecified dilution)	Monthly 4 months	> 90% regrowth	67% ITA alone; 86% for ITA + Tretinoin 0.05% cream
Kubeyinje 1994[38]	Prospective cohort	62	40 mg (nonspecified dilution)	Monthly 12 months	Complete hair regrowth	68%
Wahab 2006[26]	Prospective cohort	40	3-5 mg/mL	Monthly 3-5 months	Complete hair regrowth	65%
Kuldeep et al. 2011[15]	RCT	25	10 mg/mL	Every 3 weeks 12 weeks	> 75% hair regrowth	60%
Chang et al. 2009[31]	Retrospective case series	10	5-10 mg/mL	Every 4-6 weeks	Complete/nearly complete cosmetically acceptable	60%
Ganjoo and Tappa 2013[27]	Prospective cohort	65	5 mg/mL	Every 4 weeks 24 weeks max.	Semi-quantitative regrowth scale	47% (12 wks) 95% (24 wks)
Chu et al. 2015[9]	double-blind placebo-controlled pilot study	4	2.5 mg/mL 5 mg/mL 10 mg/mL	Every 6 weeks 36 weeks	Folliscope imaging device *	No statistically significant difference in hair density/ caliber between concentrations
Arminia et al 2015[30]	Retrospective cohort	120	5 mg/mL	Every 3 weeks 12 weeks	> 60% hair regrowth	83.3%
Devi et al. 2015[32]	RCT	113	10 mg/mL	Every 3 weeks 12 weeks	Not defined	74.3%
Kaur et al. 2015[29]	Prospective cohort	40	2.5 mg/mL	Every 3 weeks 6 weeks	> 50% hair regrowth	67.5%
Malick et al. 2018[33]	Prospective cohort	100	10 mg/mL	Monthly 3 months	> 50% hair regrowth	75%
Ustuner et al. 2017[1]	RCT	89	3.3 mg/mL 5 mg/mL 10 mg/mL	Every 4 weeks 6 months	> 75% hair regrowth	56.3% (3.33 mg/mL) 87.9% (5 mg/mL) 97% (10 mg/mL)
Barbosa de Sousa 2020[24]	Double-blind RCT	12	2.5 mg/mL	Every 4 weeks 12 weeks	Dermoscopy and photography**	38.7%

*Folliscope device CCL-215 USB, Sometech, Seoul, Korea.
**(ImageJ®).
CCT: controlled clinical trials; RCT: randomized control trials.

At 4 and 8 weeks of intervention, triamcinolone acetonide 2.5 mg/mL provided the best visual results[24].

Medium concentrations (5 mg/mL)

In 1973 Abell and Munro reported that 61% of patients with alopecia totalis treated with injections of 5 mg/mL triamcinolone acetonide using the Porto Jet needleless showed regrowth at 12 weeks, compared with 7% of control subjects injected with isotonic saline. Of those with limited AA, 92% showed regrowth at 6 weeks, but only 71% maintained regrowth at 12 weeks[13].

Frentz enrolled in the first controlled clinical trial (CCT) in 1977, using a split-body design to examine

12 patients with subtotal or universal AA. Half of the patients were treated with ITA 5 mg/mL, and the other half received contact ultraviolet radiation from a mercury arc source[25]. Half of those receiving ITA had some regrowth compared with baseline, but growth decreased over time. The other half had no noticeable hair regrowth after injections. The authors concluded that ITA inhibited spontaneous regrowth.

A more recent prospective cohort study enrolled 40 patients who had failed to respond to potent topical steroids. ITA (3–5 mg/mL, 1 mL/cm^2) was given monthly for 3–5 months. Complete hair regrowth occurred in 65% of all participants, with incomplete hair growth in a further 12%. Notably, in patients with "extensive alopecia", only 25% of the patients achieved complete hair regrowth[26].

Regarding the pediatric population, Ganjoo and Thappa studied the usefulness of ITA 5 mg/mL concentration in children with AA involving < 50% of scalp and with less than three patches. About 95% of patients showed at least 75% regrowth in the area of the patch at 24 weeks[27].

Higher concentrations (10 mg/mL)

The efficacy of ITA (10 mg/mL) was compared with topical dithranol cream in 69 patients with a single lesion of AA. The satisfactory response was classified as "uniform eruption of hair from hair follicles in the lesional skin" and was described in 84% of patients receiving ITA and 59% of patients using topical dithranol. Though, at 12 months, patients treated with the injection had a statistically significant increase in relapse rates: 57% versus 12% in patients using dithranol. As a result, the author concluded that ITA induced a better but more temporary response rate compared with dithranol[28].

Kuldeep et al. performed a randomized prospective study in 2011 which analyzed 78 patients with three or fewer patches of AA and compared hair regrowth results in three different groups- one group treated with topical betamethasone valerate foam 0.1% (n = 28), another with ITA 10 mg/mL (n = 25) and another group received tacrolimus ointment 0.1% (n = 25). Sixty percent of those treated with ITA reached the end point of > 75% hair regrowth at 12 weeks, while this occurred only in 54% of those treated with topical betamethasone valerate foam, and no patient responded in the tacrolimus group[15].

Yee et al. recently performed a systematic review and meta-analysis of all published data about the efficacy and tolerability of different concentrations of ITA for AA[3].

The rates of hair regrowth were comparable in the 5 and 10 mg/mL concentrations (80.9%, $p < 0.005$ versus 76.4%, $p < 0.005$, respectively) while lower rates of hair regrowth (62.3%, $p = 0.04$) occurred when using concentrations < 5 mg/mL[3].

In short, all studies, except one (which only included cases of extensive AA), supported intralesional steroids as a useful tool to treat AA, with varying degrees of success[25]. This treatment option seems to be more effective in patients with limited alopecia and shorter disease duration[1,8].

ITA concentrations assessed varied from 2.5 to 10 mg/mL. Five studies included lower concentrations (2.5-3.3 mg/mL), with response rates ranging from 38.7 to 67.5%[1,9,24,26,29]. Seven studies analyzed ITA concentrations of 5 mg/dL, with success rates ranging from 50 to 95%[9,13,25–27,30,31], and eight studies analyzed 10 mg/dL concentrations of ITA, with response rates of 60-84%[1,9,14,15,28,31-33]. However, variations in method and frequency of administration limit the comparison of results between different studies.

The lack of consensus on this topic is explained, in part, by discrepancies regarding the definition of response (although the majority defined response to treatment as > 50% hair regrowth), as well as disparities among the characteristics of patients (different ages, gender, extent, and duration of alopecia). The scarcity of a standardized technique of injection and the absence of a placebo arm to control for spontaneous hair regrowth further contributes to this dilemma.

Furthermore, most studies compare the efficacy of ITA with other (non-injected) treatments or other injected steroids, with just four of them comparing the effectiveness of different concentrations of ITA[1,3,9,24].

Side effects

Skin atrophy at the site of injection is a consistent side effect of IL corticosteroid therapy. The risk is particularly high when higher concentrations or higher volumes are injected in the same site, but this usually resolves after a few months. The wrong technique (e.g., injection in subcutis) may also contribute to some cases of atrophy[2].

In their study, Ustuner et al.found cutaneous atrophy ratio after 6 months significantly superior in TA group compared to BD groups (85.7% vs 22.2%)[1].

Yee et al.described this side effect in 3.33% of subjects treated with 5 mg/mL concentration and 20% of subjects treated with 10 mg/mL[3].

Apart from skin atrophy, one should also be aware of the risk of cataracts and raised intraocular pressure when corticosteroids are injected close to the eye. Anaphylaxis has been reported in two patients receiving TA for treatment of alopecia areata[2]. Another rare complication is perilymphatic cutaneous atrophy[34].

Other reported side effects include slight discomfort and hemorrhage at the injection site, pustule, and folliculitis, and minor depression on plasma cortisol the day following triamcinolone injection[1,13].

Notably, there are some cases of glucocorticoid resistance in AA, which may be explained by decreased expression of thioredoxin reductase 1 in the outer root sheath[35,36].

Conclusion

Based on the existing research, concentrations of ITA between 5 and 10 mg/mL may offer the greatest benefit to patients with focal AA.

Using the lowest effective concentration minimizes local side effects of skin atrophy and likely reduces the potential for systemic absorption, allowing the treatment of more extensive scalp areas[9]. Therefore, the authors agree that ITA 5 mg/mL may have a better risk-benefit profile for scalp AA. Lower concentrations have proved to be less useful in most of the studies, unless when injecting the face (eyebrows/ beard) where these concentrations may be safer[17].

Regardless of all the described studies, randomized controlled trials using a standardized technique are still needed to improve decision-making and better understand the individual and perceived benefits, risks, and tolerability of different concentrations.

What does this study add?

Triamcinolone acetonide is the first line of intralesional corticosteroid therapy for patients with limited, patchy alopecia areata.

Most of the existing literature compares intralesional triamcinolone acetonide with other (non-injected) treatments or other injected steroids. Just four studies compare the effectiveness of different concentrations of intralesional triamcinolone acetonide.

According to the current literature, concentrations of 5 mg/mL seem to be the best treatment choice for scalp AA, and lower concentrations can be advised when injecting the face.

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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REVIEW ARTICLE

Drugs and alopecia

Fármacos e alopecia

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Abstract

Drugs are a relatively common cause of diffuse, nonscarring hair loss. They may interfere with the normal hair cycle, either by an abrupt cessation of the mitotic activity of matrix cells, causing anagen effluvium, or by an interruption of the anagen and a premature passage to the telogen phase, originating telogen effluvium. It is essential to obtain a complete history, including previous diseases and medications, focusing on the past 3 months, in order to rule out possible drug-induced alopecia. This review encompasses the most frequently involved drugs, including mechanisms of action and clinical characteristics of drug-induced alopecia. The correct recognition of drug-induced alopecia is essential since the main approach is to stop the offending agent, whenever it is possible.

Keywords: Alopecia. Hair loss. Telogen effluvium. Anagen effluvium. Nonscarring alopecia. Drugs.

Resumo

Os fármacos são uma causa relativamente comum de deflúvio e alopecia difusa, não-cicatricial. Podem interferir com o normal ciclo capilar, quer por uma paragem *abrupta* da atividade mitótica das células da matriz do folículo piloso, originando deflúvio anagénico, quer por uma interrupção da anagénese e uma transição prematura para a telogénese, provocando deflúvio telogénico, e, por vezes, alopecia difusa não-cicatricial. É essencial obter uma história clínica completa, incluindo doenças e fármacos prévios, particularmente nos últimos três meses, de modo a descartar uma possível alopecia induzida por fármacos. Esta revisão engloba os principais fármacos causadores de alopecia, incluindo mecanismos de ação e características clínicas. O correto reconhecimento de alopecia induzida por fármacos é essencial, uma vez que a abordagem principal é suspender o agente imputável, quando possível.

Palavras-chave: alopecia, queda de cabelo, deflúvio telógenico, deflúvio anagénico, alopecia não-cicatricial, fármacos

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Introduction

The hair cycle is composed of three stages: anagen (growth), telogen (resting), and catagen (transition from anagen to telogen). Hair follicle activity varies according to the body region and even in the same area, meaning that each follicle has its own cycle[1]. The normal duration of scalp anagen hairs ranges from 2-6 years, with an average of 3 years. Catagen only lasts 2-3 weeks, followed by telogen, where the follicle remains for 3-6 months. In normal conditions, around 86% of the hairs are in the anagen, 13% in telogen, and 1% in catagen[1]. Many factors, including genetics, the immune system, hormones, or drugs may interfere with the normal hair cycle[2]. Telogen effluvium may lead or not to diffuse alopecia depending on the intensity and duration of the shedding.

Alopecia can be divided into scarring or nonscarring. Drugs interfere with the hair cycle by one of the two mechanisms: an abrupt cessation of mitotic activity of the matrix cells, originating anagen effluvium; or interruption of the anagen phase and induction of a premature passage of the follicle from the growth phase do the resting phase, originating telogen effluvium[3].

Anagen effluvium, due to drugs mainly used in chemotherapy, leads to nonscarring, reversible alopecia[4]. There is a sudden hair loss, since the anagen phase is interrupted, which is observed 1-3 weeks after the initiation of the drug. It usually reverts after 3 months of the drug's cessation[3,4].

Telogen effluvium is the most common type of diffuse hair loss, and it occurs when the hair cycle is interrupted, inducing an abnormal amount of anagen hairs to rapidly enter the telogen phase[3]. The hair loss usually occurs 2-4 months after the administration of the inciting drug (time for a hair follicle to progress through the telogen and be shed)[4]. Techniques such as trichogram, phototrichogram and, rarely, scalp biopsy help to confirm the diagnosis when more than 20% of the hairs are in telogen (although more than 15% is already suggestive), in the absence of inflammation or scarring[3]. Several medications induce telogen effluvium.

Main drugs

Anticoagulants

Different classes of anticoagulants, such as heparin and its derivates[5,6], vitamin K antagonists[7] and, more recently, new oral tyt anticoagulants (NOACs)[8,9] have been reported to induce alopecia. The underlying mechanism is poorly understood. On one hand, it is known that minoxidil increases the secretion of different growth factors, including platelet-derived endothelial cell growth factor[10]. On the other hand, anticoagulation is a recognized cause of platelet aggregation dysfunction, which in turn may also cause a dysfunction of platelet beneficial properties for hair growth[9,11].

Heparin and low-molecular-weight heparins, including enoxaparin and tinzaparin, can cause telogen effluvium, which seems to be more related to the total dose than to the duration of treatment, and reverts with cessation of therapy[5,6]. Vitamin K antagonists, namely warfarin, have been reported to cause reversible alopecia in up to 40% of patients, possibly due to a forced early entry into the telogen phase[7,12].

In 2020, a study comparing different reports of alopecia induced by NOACs with both positive and negative controls (known drugs of causing alopecia or not, respectively), demonstrated a significant over-reporting of alopecia associated with rivaroxaban, apixaban, edoxaban, and dabigatran[9]. Of the four agents, rivaroxaban was the most frequently involved and dabigatran was the least. These differences might be related to their slightly different mechanisms of action. While rivaroxaban binds directly to factor Xa, dabigatran acts through antithrombin III, which is the same mechanism as fondaparinux[12]. This last drug was used as a substitute for rivaroxaban and apixaban in a case of diffuse hair loss with good results[12].

Antihypertensive drugs

Both beta-adrenoceptor antagonists (β-blockers) and angiotensin-converting enzyme (ACE) inhibitors, commonly used to treat hypertension, have been reported to cause alopecia[2].

Keratinocytes contain adrenergic receptors, mainly of the β2 subtype, which are densest at the basal layer and scarcer at the stratum corneum, correlating with keratinocyte differentiation[13]. These may be implied in different adverse cutaneous reactions related to β-blockers, which have been recognized as a cause of alopecia, probably due to a direct toxic effect on the hair follicle[14].

Telogen effluvium has been described after the use of topical timolol in patients with glaucoma, which remitted following drug discontinuation[14,15]. Although it is a topical medication, ophthalmic β-blockers enter the bloodstream through the lacrimal system, increasing their levels in the blood and inducing systemic reactions[15]. A case of patchy alopecia involving the scalp, arms, and chest induced by propranolol was also described. After the withdrawal of the drug, there was complete resolution of the alopecia, which recurred with a re-challenge[16].

Regarding ACE inhibitors, captopril is one of the most implied in inducing diffuse hair loss[2]. The underlying mechanism may be related to zinc deficiency caused by captopril since ACE is a zinc-containing molecule[17]. In fact, zinc supplementation has been reported to reverse the side effects of captopril due to zinc deficiency, such as loss of taste and alopecia[18]. Besides this, a case of alopecia, with normal serum zinc levels, starting 4 months after the beginning of captopril, was reported, suggesting an alternative mechanism[18].

Antimicrobials

Diverse antifungals have been the cause of diffuse hair loss, namely terbinafine[19], fluconazole[20], itraconazole,[21] and albendazole[22].

Terbinafine has been reported to induce acute telogen effluvium, confirmed by trichogram, 3 months after starting the drug, which resolved with its withdrawal[19].

A retrospective study described the occurrence of scalp alopecia in 33 patients medicated with fluconazole[20]. Of note, 88% of these patients were taking high doses (> 400 mg per day) of the drug for the treatment of systemic mycoses, leading to the assumption that this side effect may be dose-related.

Albendazole has been reported to cause anagen effluvium most commonly in long-term or high-dose usage,[23] but the occurrence of alopecia after 2 weeks from the beginning of the treatment has been reported[22]. The underlying mechanism may be related to the antiproliferative effects of albendazole, namely it's capacity to inhibit cellular microtubule polymerization binding to β-tubulin[23].

Isoniazid has also been reported to cause diffuse hair loss 1 month after its initiation for the treatment of tuberculosis[24].

Regarding antiretroviral drugs used for the treatment of human immunodeficiency infection, indinavir has been reported to cause both telogen effluvium and patchy alopecia in up to 10% of the patients[25]. Combination therapy with more than one antiretroviral may be associated with more serious hair loss[4].

Antithyroid drugs

Hypothyroidism is associated with telogen effluvium as well as dry and brittle hair[26]. Along with alopecia areata, patients with chronic telogen effluvium seem to demonstrate a higher prevalence of anti-thyroperoxidase antibodies, compared to the normal population[27].

Hair follicles express thyroid hormone receptors, where both triiodothyronine (T3) and thyroxine (T4) seem to modulate multiple hair follicle functions, including epithelial cell proliferation, apoptosis, and keratin expression[28]. Following this, it is not surprising that overtreatment with antithyroid drugs is a cause of hair loss. However, drugs like carbimazole and thiouracil have been reported to cause telogen effluvium even in euthyroid patients[29].

Anti-tumor necrosis factor alpha (TNF-α) and other biologic agents

Psoriasiform eruption induced by anti-TNF-α agents has an incidence ranging from 1.5 to 5%, but scalp involvement with associated alopecia is usually rare[30,31]. The underlying mechanism might be related to the blocking of TNF receptors, increasing the production of interferon-α by plasmacytoid dendritic cells, which will activate pathogenic T lymphocytes[32]. Most frequently the alopecia presents as inflammatory and nonscarring, although cases of alopecia areata-like and scarring alopecia have been described[33,34]. Histological findings are similar to the ones observed in psoriasis, such as acanthosis with hyper or parakeratosis and a variable number of neutrophils in the epidermis, as well as dermal lymphocytic infiltrate[33]. Occasionally, alterations resembling alopecia areata are also observed, namely an increase in telogen hairs and prominent peribulbar lymphocytic infiltrate[34].

More rarely, cases of psoriasiform alopecia induced by anti-interleukin (IL)—12/23 and anti-IL-17 agents have been reported[35,36]. Clinical and histological features were comparable to those observed in the context of anti-TNF-α therapy.

The suspension of the offending drug is not mandatory and depends on the baseline condition and the severity of the lesions. Psoriasiform alopecia can be managed with topical treatments, such as corticosteroids, calcineurin inhibitors or vitamin D analogs, or systemic therapies, namely cyclosporin or methotrexate[33]. Regarding anti-TNF-α, switching to an alternative agent of the same class may also be helpful[37].

Contraceptives

Hormones play an important role in the progression of the hair cycle, although most of the precise mechanisms behind this modulation still need to be elucidated[38].

Oral contraceptives are implicated in hair loss in two different ways: either due to the androgen activity caused by the progestin component (rare) or to the lack

of mild anti-androgen activity following the interruption of long-term contraceptive therapy (very frequent)[39].

Apart from its interaction with progesterone receptors, progestins also interact with androgen receptors. First-generation (norethisterone) and second-generation (levonorgestrel) progestins show higher affinity to androgen receptors, causing androgenetic alopecia in susceptible women. On the other hand, third-generation progestins (desogestrel, norgestimate, and etonogestrel), drospirenone, and cyproterone acetate have little androgenic or even mild antiandrogenic activity[40]. Progestin implants and intrauterine devices have also been reported to cause alopecia, representing a common cause for the removal of these devices[41,42].

Estrogen, present in combined oral contraceptives, may be responsible for hair growth by extending the anagen phase. This is supported by the fact that after menopause, with the decrease in estrogen levels, women are indeed more prone to develop alopecia[43].

The discontinuation of drugs that prolong the anagen phase, such as oral contraceptives, results in telogen effluvium due to the advance of the follicle into a premature rest[44]. Probably, it is the most common cause of drug-induced alopecia.

Oral contraceptives may have a protective role in the development of frontal fibrosing alopecia, supported by a study with 105 women and 100 controls, where a history of oral contraceptives was significantly greater in the control group[45]. This protection was also verified for intrauterine devices[46].

Cytostatics, immunotherapy, and targeted therapy agents

Alopecia is the most frequent dermatologic side effect of cytostatics, with an estimated incidence of 65%, and it is considered one of the most traumatic aspects of chemotherapy[47].

These agents preferentially target mitotically active cells, inducing cellular stress and subsequent apoptosis. The cells of the hair matrix are among the fastest dividing cells in the human body and therefore are greatly affected by chemotherapeutics, especially if they are in the anagen phase. Catagen and telogen follicles, in contrast, are mitotically quiescent and are relatively spared. As up to 90% of the human scalp is in the anagen phase at a given time, a single dose of chemotherapy can induce widespread follicular damage[48]. It affects mostly scalp hairs because other locations such as eyebrows, eyelashes, axillary and pubic hairs have a lower percentage of anagen hairs[49].

Anagen effluvium is most frequent and severe in patients treated with polychemotherapy, with alkylating agents, antimetabolites, vinca alkaloids, and topoisomerase inhibitors representing the main offenders[50,51]. The degree of hair loss is dependent on the route, dose, and schedule of the chemotherapy and it usually begins 1-3 weeks after the beginning of treatment[52].

Permanent alopecia, lasting more than 6 months after the completion of chemotherapy, has been described as a separate entity[53]. It is more common after high-dose busulfan-containing treatments[54-57], although it can also result from repeated courses of cyclophosphamide and carboplatin or from therapy with taxanes (docetaxel and paclitaxel) for breast cancer[58,59]. Interestingly, a clinicopathological study of patients with permanent diffuse alopecia demonstrated a nonscarring pattern on histologic examination, with an increased number of telogen follicles[47]. This may be explained by both synchronizations of the hair follicle cycling, which follows hair regrowth after anagen effluvium, and a shortening of the hair cycle of follicles that underwent miniaturization. In this setting, a proposed hypothesis for permanent chemotherapy-induced alopecia may be that the drugs precipitate androgenetic alopecia in predisposed individuals. Another theory is the reduction of the stem cells' population in the bulge or papilla[47].

Pharmacological therapies for chemotherapy-induced alopecia include topical and oral minoxidil, although it is not effective in preventing it[60]. This topic will be discussed in more detail in the Management section.

Alopecia areata is part of the frequently described immune-related adverse events, occurring in the context of immunotherapy. Both anti-T-lymphocyte-associated protein 4 (CTLA-4) and anti-cell death protein 1 (PD-1) agents are reported to induce alopecia areata, including the universalis type, in 1-2% of the patients[61,62].

Targeted therapies work by blocking oncogenic pathways implied in cell growth and survival. BRAF and mitogen-activated protein kinase (MEK) inhibitors may frequently induce alopecia, with an incidence of 23.7% for vemurafenib, 18.9% for dabrafenib, and 13.3% for trametinib[63,64]. Both mild diffuse and scarring alopecia have been described with epidermal growth factor receptor inhibitors[65]. The latter has been reported in 5% of patients treated with cetuximab[65], and it can be secondary to folliculitis *decalvans* or erosive pustular dermatosis of the scalp[66,67].

Interferon

Interferon (IFN) related alopecia include telogen effluvium, dystrophic anagen effluvium, alopecia at the injection site, and alopecia areata[68].

A case of dystrophic anagen effluvium confirmed by histopathological examination was reported in a patient treated for hepatitis C virus with pegylated-IFN plus ribavirin, which reverted almost 1 year after stopping the treatment[69].

Multiple cases treated with IFN-α developed patches of alopecia on the scalp, which progressed to alopecia areata universalis. In fact, IFN has been linked to the exacerbation or the occurrence of several types of autoantibodies or autoimmune diseases, including thyroid disorders and insulin-dependent diabetes mellitus, or diseases involving altered cell-mediated immune functions, such as pneumonitis, nephritis, and colitis[68,70].

Telogen effluvium also occurs in up to 50% of the patients, it is not dose-related and regresses with cessation of therapy[4].

Minoxidil

Minoxidil has pro-mitotic effect on hair follicle cells, as well as anti-androgen, anti-inflammatory, and vasodilator properties, inducing the Wnt/β-catenin pathway and affecting the length of the anagen and telogen phases[71]. Withdrawal of topical or systemic minoxidil can, in turn, cause telogen effluvium due to the simultaneous entry of all the follicles, which extended their growth under the effect of the drug, to telogen phase[4]. On the other hand, some patients will have telogen effluvium at the beginning of minoxidil treatment, which may be caused by the induction of the anagen phase on hair follicles with a subsequent detachment of the old club hair[72]. This fact should be carefully explained to the patient.

Psychotropics

Psychotropics, including mood stabilizers and antidepressants, can induce hair loss by affecting the telogen phase of the hair cycle[2].

Lithium causes telogen effluvium in 12-20% of long-term users, along with hair thinning, which can be even more frequent[4,73]. The exact mechanism of hair loss is still unknown, although it can also occur in the context of lithium-induced hypothyroidism. For that reason, thyroid function must be also checked in these patients[2].

Diffuse alopecia arises in up to 8-12% of the patients treated with sodium valproate, in a dose-dependent manner[74]. The underlying mechanism seems to be related to biotin and/or zinc deficiency induced by the drug[75,76]. Although the exact pathogenesis is not entirely understood, oral supplementation with biotin and zinc improves alopecia after 3 months[75].

Telogen effluvium is also common in patients medicated with selective serotonin reuptake inhibitors, especially fluoxetine, but also paroxetine and sertraline to a lesser extent[4,77].

Retinoids

Retinoids function by binding nuclear receptors, which in turn interact with other transcription factors to coordinate gene expression. A study has found that hair loss during systemic therapy with retinoids may be provoked by inhibition of hair shaft formation during anagen and induction of premature catagen, along with significant inhibition of keratinocyte proliferation and a slight stimulation of apoptosis in the matrix of anagen hair bulbs[78].

Isotretinoin and acitretin can induce telogen effluvium with visible alopecia in up to 20% of the patients, which seems to be dose-related[4]. Few cases may be persistent and severe[4,78], or even associated with agranulocytosis, suggesting a common underlying mechanism, such as hair cycle arrest[80]. Fortunately, in this last case, the side effects were reversed with drug withdrawal.

Management

Drug-induced alopecia more frequently involves the scalp and presents as diffuse and nonscarring. In the context of chemotherapy, the occurrence of permanent alopecia is a possibility, but not rule[2].

For a patient with diffuse hair loss, a complete history, including previous diseases, medication, and weight loss, focusing on the previous 3 months, should be taken carefully. Moreover, pull test, trichoscopy, and sometimes (photo) tricogram are valuable techniques that may help differentiate telogen effluvium from other types of alopecia, namely androgenetic alopecia. On the other hand, anagen effluvium is usually easier to diagnose due to the acute and severe onset and the presence of dystrophic hairs on trichoscopy[4]. Further investigation may include complete blood count, thyroid function tests, serum vitamin D, iron profile, or even more specific laboratory parameters according to the patient's history (e.g., serum proteins, vitamin B_{12}, or zinc, if the nutritional deficit is suspected), in order to rule out other causes of diffuse hair loss[39,81].

In drug-induced telogen effluvium, discontinuation of the offending drug will gradually cease hair loss after 2-3 months[4]. The complete recovery of hair volume may take much more time, and this fact should be told to the patients. Nutritional supplements may have a role in promoting hair growth and maintaining its structure[81].

Chemotherapy-induced alopecia may have a slightly different approach. A limited number of effective prevention strategies have been reported, including scalp-cooling techniques, although with variable results and indications[82,83]. Despite the lack of benefit in preventing chemotherapy-induced alopecia, topical and oral minoxidil may help by reducing the time of hair regrowth[48].

Conclusion

In the presence of diffuse hair loss, especially telogen effluvium, a high index of suspicion should be maintained regarding medications, especially if other causes have been excluded. The initial treatment with the responsible drug should be searched 3-4 months before the beginning of the effluvium. In most cases, drug discontinuation will stop shedding in some months. The complete recovery of hair volume will take longer.

This article aims to raise awareness among clinicians of the most frequent drugs involved in diffuse alopecia.

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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REVIEW ARTICLE

Strongyloides stercoralis and immunosuppression in dermatology

Strongyloides stercoralis e a imunossupressão na dermatologia

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Abstract

Dermatologists can take advantage of numerous immunosuppressive drugs to treat several conditions such as autoimmune bullous dermatoses, psoriasis, and connective tissue diseases. In particular, corticosteroids often play an important role in the management of these diseases. However, prior to the start of immunosuppressive therapy, screening for opportunistic infections is crucial. Strongyloidiasis is one such disease. The parasite *Strongyloides stercoralis* is a nematode with a complex life cycle and the ability to autoinfect its host. Although it currently is a rare disease in Portugal, it has a widespread distribution especially amongst low-income countries. It is usually responsible for a chronic asymptomatic infection, albeit frequently with intermittent eosinophilia. Certain comorbidities may increase the risk for hyperinfection or disseminated disease. Such factors are the presence of immunocompromising conditions such as haematological malignancies, AIDS, HTLV-1 infection and therapies such as transplantation and corticosteroids. The screening and diagnosis are usually performed with parasitological and serological tests, and the treatment of choice is ivermectin. As such, since chronic infection can be asymptomatic and hyperinfection potentially lethal, screening prior to the start of immunosuppressive treatment is imperative. Dermatologists that prescribe such regimens should be familiar with the need of parasite screening and management prior to the start of therapy.

***Keywords*:** Strongyloidiasis. *Strongyloides stercoralis*. Corticosteroid therapy. Immunosuppression in dermatology. Immunosup pression. Hyperinfection syndrome.

Resumo

A Dermatologia tem à sua disposição inúmeros fármacos imunossupressores para tratar várias doenças como dermatoses bolhosas autoimunes, psoríase e doenças do tecido conjuntivo. Em particular, a corticoterapia tem um papel frequentemente importante na gestão destas patologias. No entanto, previamente ao início da terapêutica imunossupressora, o rastreio de infeções oportunistas, como a estrongiloidíase, é crucial. O parasita *Strongyloides stercoralis* é um nematoda com um ciclo de vida complexo e com a capacidade de provocar autoinfeção no hospedeiro. Apesar de ser atualmente uma doença rara em Portugal, tem uma distribuição generalizada, sobretudo em países de baixo rendimento económico. Geralmente, é responsável por uma infeção crónica e assintomática, se bem que frequentemente com eosinofilia intermitente. Certas comorbilidades

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podem aumentar o risco de hiperinfeção ou doença disseminada. Estes fatores são a presença de certas patologias com compromisso do sistema imunitário, como neoplasias hematológicas, Sida e infeção pelo HTLV-1. Também certas intervenções, como a corticoterapia ou a transplantação, são fatores de risco. O rastreio e diagnóstico fazem-se habitualmente com testes serológicos e parasitológicos, e o tratamento de escolha é a ivermectina. Assim, dado que a infeção crónica pode frequentemente ser assintomática e a hiperinfeção potencialmente letal, o rastreio prévio ao início de tratamento imunossupressor é fundamental. Neste contexto, Dermatologistas que prescrevem tais fármacos devem estar familiarizados com a necessidade de rastreio para a infeção por este parasita e sua gestão antes do início da terapêutica.

Palavras-chave **:** Estrongiloidíase. *Strongyloides stercoralis*. Terapêutica corticosteroide. Imunossupressão em dermatologia. Imunossupressão. Síndrome de hiperinfeção.

Introduction

Dermatologists have at their disposal numerous immunosuppressive drugs that are useful in controlling several conditions such as autoimmune bullous dermatoses, psoriasis, and connective tissue disease[1,2]. Indeed, it is imperative that physicians are aware of the iatrogenic increased risk and severity of infection. As such, screening for several latent microorganisms can be valuable (e.g., tuberculosis, hepatitis B and C, deep fungal infections, or HIV)[1,2].

One such parasite is *Strongyloides stercoralis*. It is a skin-penetrating intestinal nematode with a complex life cycle[3]. It is widely distributed around the world especially around the tropics[3] and is one of the few helminths with the ability of autoinfection[4]. Since it can present as a hyperinfection syndrome that occurs especially among patients with immunosuppressive conditions or therapies[4–6], it is relevant to refresh its epidemiology and pathology, with a focus on the role of its screening prior to the start of immunosuppressive therapy.

Epidemiology

Strongyloidiasis is an emerging infection with a worldwide incidence underestimated in many countries[7]. It has an estimated global prevalence of over 350 million people[8]. While it has been traditionally described among patients from tropical and subtropical countries[3,9], the prevalence of infection has been increasing not only in Caribbean, Southeast Asia, Latin America, and sub-Saharan Africa, but also in southern, eastern, and central Europe[6,9]. While Portugal is currently considered a nonendemic country, with infection with *S. stercoralis* being found especially among immigrants from endemic countries, the prevalence of strongyloidiasis and other helminthiasis was higher during the first three quarters of the 20th century, likely due to a lack of basic sanitation conditions[10]. During this time, *S. stercoralis* was found especially in the regions between the Douro and Tagus rivers[10], and even very recently, a case of a Portuguese woman presenting with strongyloidiasis was reported[9], even though likely infected long ago[11]. Moreover, in 2001, in a cohort of children from Lisbon, 0.9% were found to be infected[12].

In many endemic areas, where moist soil, temperate or tropical climate and improper disposal of human waste coexist, the prevalence of strongyloidiasis can reach 50%. This is especially the case in West Africa, the Caribbean, Southeast Asia, Brazil, Cambodia, and some regions of Spain. Nevertheless, Southeast Asia seems to have the highest endemic prevalence[13,14]. Other risk factors for infection include white males, working with soil and travellers to areas of endemicity[6]. Although strongyloidiasis occurs in all ages, infection usually happens in childhood, since children are more likely to play outdoors with higher exposure to contaminated soil[12,15].

Patients with certain immunosuppressive conditions are also at a higher risk for strongyloidiasis. Indeed, an altered cellular immunity (especially those on long-term corticosteroid therapy, but also human immunodeficiency virus [HIV] infection/acquired immunodeficiency syndrome), certain hematological malignancies and therapies (such as those for lymphoma and allograft transplant recipients) are at a higher risk for severe strongyloidiasis infection[5,16,17]. Human T-lymphotropic virus type 1 (HTLV-1) infection is also related to *S. stercoralis* with increased prevalence of this parasite in overlapping endemicity areas[3,18]. Indeed, corticosteroid treatment and HTLV-1 infection are the two conditions most associated with hyperinfection[16].

Lifecycle and transmission

Strongyloides stercoralis has a complex life cycle with two unique and distinct cycles (Fig. 1). While transmission usually occurs through contact with contaminated soil, person-to-person transmission has been described, especially among men who have sex with men[19].

As one of the few helminths that is able to autoinfect its human host[20], rhabditiform larvae can fertilize into

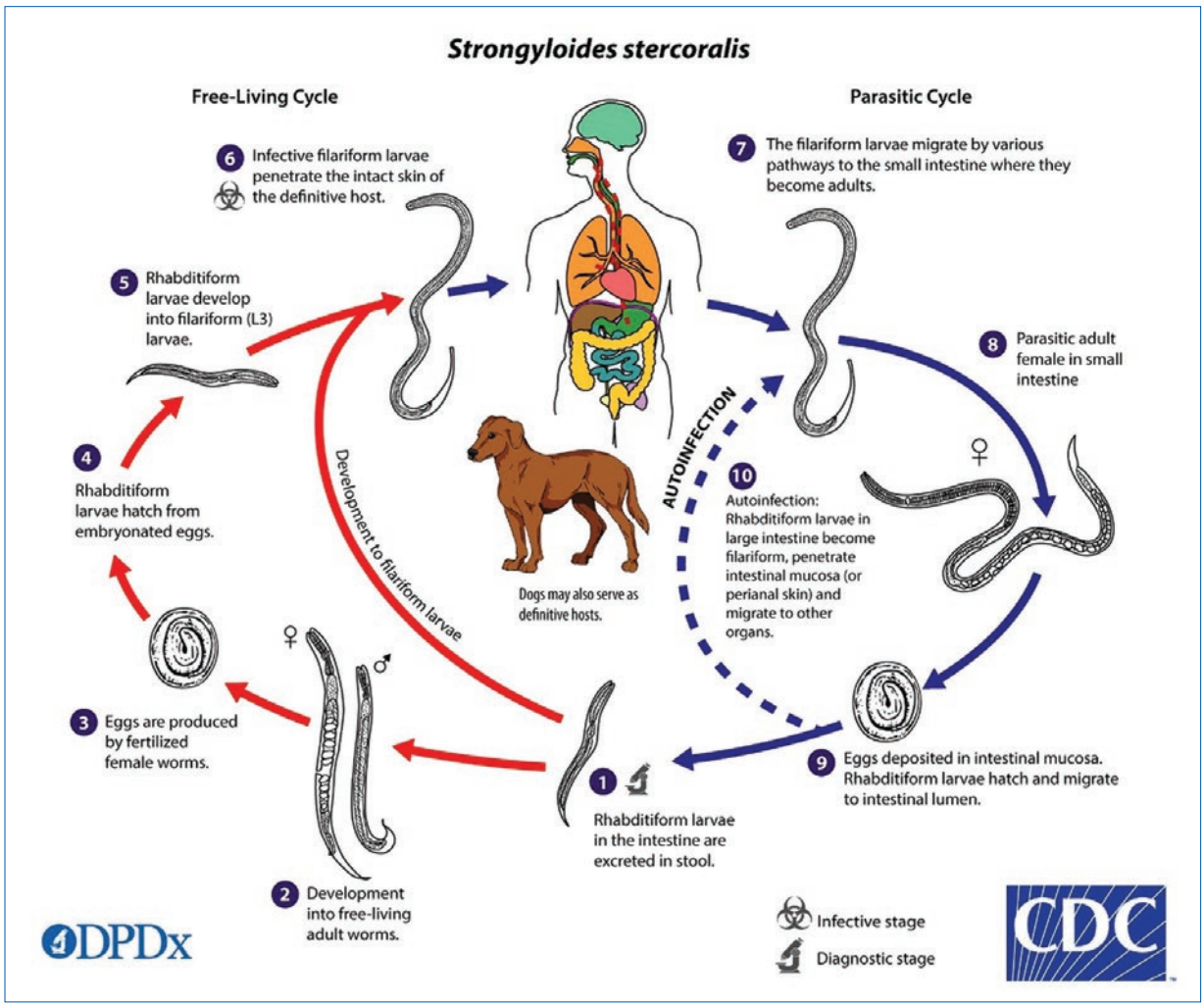

Figure 1. Strongyloides *stercoralis* life cycle (Image from courtesy of DPDx, a website by the Centers for Disease Control and Prevention (CDC)'s Division of Global Health, Parasitic Disease and Malaria)[54]. It consists of a free-living cycle in the soil, where both males and females coexist and maintain infestation in the ground. Here, eggs are hatched as rhabditiform larvae and afterward transformed into infective filariform larvae. In this stage, the larvae penetrate the skin and migrate to the small intestine where they mature into adult females and produce eggs parthenogenetically. These hatch into rhabditiform larvae that are excreted in the stool and can lead to autoinfection. These parasitic females may live up to five years, continuing their reproductive cycle[6,18,20].

its filariform stage in the large bowel. Afterwards they migrate through the lymphatic and venous circulation, reaching the pulmonary circulation, alveolar space, and crawling up the respiratory tract. Then they return to the intestine through swallowed sputum[6,18]. External auto-infection can also occur, in which case it often leads to the development of larva currens[6].

Almost all strongyloidiasis are due to infection with *Strongyloides stercoralis*. However, the primate parasite *Strongyloides fulleborni* has been described in children in Africa and in Papua New Guinea, where it is a cause of "swollen belly syndrome"[20].

Pathogenesis and clinical manifestations

Strongyloides stercoralis infection was first described in 1876 from the stool of French soldiers with diarrhea who were returning from the old Indochina region, leading to the designation of "Cochin-China diarrhoea"[21]. Manifestations of primary acute infection with *Strongyloides stercoralis* are directly related to its life cycle. After skin penetration, if the larvae do not find their natural route to the circulation and stay in the integument, larva migrans presenting as a maculopapular, pruriginous and serpiginous rash can occur[22].

Table 1. Principal manifestations of acute and chronic strongyloidiasis[7,9,20,22,23,26,55]. Strongyloidiasis presentation directly relates to the parasite's life cycle. Acute infection can be asymptomatic in up to one-third of infections. Chronic strongyloidiasis is often asymptomatic, with eosinophilia being the sole, albeit intermittent, marker. Otherwise, gastrointestinal symptoms can occur, with larva currens, abdominal pain, and diarrhea being a classically recognized triad

	Acute strongyloidiasis	Chronic strongyloidiasis
Gastrointestinal manifestations	• Abdominal pain, malabsorption, steatorrhea, diarrhea • Onset usually 2 weeks after infection; larvae found on the stool after 3-4 weeks	• Diarrhea, malabsorption, steatorrhea, constipation, abdominal pain, intermittent vomiting
Respiratory manifestations	• Cough, wheezing, shortness of breath, tracheal irritation, bronchitis, Loeffler's syndrome, transient pulmonary infiltrates • Onset a few days after infection	• Cough, dyspnoea, recurrent asthma • Often mild or absent
Other	• Larva migrans, fever, anorexia • Eosinophilia (as high as 75-80%)	• Intermittent eosinophilia and elevated IgE levels, often isolated • Nephrotic syndrome • Pruritus ani, larva currens, urticarial, petechial and purpuric rashes

Manifestations of acute and chronic strongyloidiasis can be found in Table 1. Chronic infection is often asymptomatic, with eosinophilia being the sole, albeit intermittent, marker[9,23]. Actually, hypersensitivity is an important part of the immune response to this parasite, contributing both to the pathogenesis of the disease and to its protection[16]. In fact, a primary Th2 response favors infection by increasing tissue permeability to the parasite and reducing complement activation, important for the larvae-killing capabilities of eosinophils and granulocytes[24,25], but interleukin-13 causes increased peristalsis, possibly leading to increased larval expulsion[25]. On the other hand, HTLV-1 infection, a known risk factor for severe strongyloidiasis, results in an increased interferon-gamma production and decreased levels of interleukin-4 and IgE, which creates a favorable environment for *Strongyloides stercoralis* proliferation[16].

Whereas internal autoinfection is usually less relevant in healthy individuals, in immunosuppressed patients it can present as one the two most severe forms of strongyloidiasis, either the hyperinfection syndrome or the disseminated disease. Although immunocompetent patients are also at risk, those with impaired cell-mediated immunity are much more susceptible[6,26]. In severe strongyloidiasis in the immunocompromised host, eosinophilia is often absent[23]. In the hyperinfection syndrome there is a favorable environment for parasitic proliferation, resulting in an increased burden along the usual migration pattern. It essentially is an accelerated auto-infection and the distinction between these two is merely quantitative and not strictly defined[26].

As such, new onset or exacerbation of gastrointestinal and pulmonary symptoms is frequent, and the identification of increased numbers of larvae in faeces and/or respiratory samples is the hallmark of hyperinfection[26]. While the increased numbers can lead to complications such as intestinal obstruction, ileus, and gastrointestinal bleeding, usually there is no metastatic dissemination outside the regular migration pattern. Nevertheless, migration of larvae that carry bacteria on the surface of the larval integument, as excreta from the larval intestinal tract[27] or the presence of ulcers may facilitate the spread and systemic infection with enteric bacteria[26].

Pulmonary complications including pulmonary infiltrates, diffuse alveolar hemorrhage, and respiratory failure can develop in patients with hyperinfection syndrome and, if not treated, may be lethal. Indeed, a lack of familiarity with this parasite leading to delayed screening and treatment is a cause for a high mortality among immunosuppressed patients[28].

While hyperinfection denotes an increased parasite replication, disseminated strongyloidiasis implies widespread dissemination to extraintestinal organs, without the obligatory need for an increased parasite proliferation or severity of disease[26]. Multiple organs beyond the range of its normal life cycle are affected, including the liver, heart, kidneys, and central nervous system[6]. In severe disease, and as in hyperinfection, translocation of enteric bacteria can occur, leading to polymicrobial bacteriemia or meningitis[6]. Cerebrospinal fluid analysis shows neutrophilic pleocytosis with an elevated protein level and low glucose level. A gram stain can be positive for enteric bacteria and direct examination can reveal *Strongyloides stercoralis* larvae[29,30].

Other manifestations include lymphadenopathy, fever, haemoptysis, cough, anaemia, vomiting, weight loss, abdominal pain, and distension[31]. Since it coexists frequently with hyperinfection syndrome in the immunosuppressed patient, its manifestations may overlap[6].

Diagnosis

Since most patients with strongyloidiasis do not present with distinct clinical features, the diagnosis requires a high degree of suspicion[11].

Strongyloides stercoralis larvae can be intermittently found in faeces usually a month after skin penetration. Usually, only larvae are found since the eggs immediately hatch in the intestine. *Strongyloides fulleborni*, however, sheds eggs in faeces, and is readily found using microscopy[6]. Direct smear examination of stool in saline and Lugol's iodine stain is a definitive diagnostic testing, although with a low sensitivity (as low as 21%). However, concentration methods, such as formalin-ethyl acetate, Harada-Mori techniques, and Baermann concentration increase the yield and are significantly more sensitive[32,33]. While diagnosis of hyperinfection is relatively easy due to the high quantity of larvae in stool and sputum, outside of this setting it is often inadequate, as a single stool examination is less than 50% sensitive for making diagnosis[34]. As such, it is mandatory to screen multiple times, ideally using a concentration method, although they are seldom performed in most parasitology labs[34,35]. A sensitivity higher than 90% can be achieved if seven or more samples are examined[35]. When concerning the hyperinfection syndrome, the examination of a duodenal aspirate for eggs and larva is the most sensitive diagnostic procedure (as high as 90%)[31].

In addition to faeces samples, endoscopic examination and biopsies can be useful. Endoscopy may range from normal-appearing mucosa to severe duodenitis or colitis with oedematous and erythematous mucosa and white villi. Moreover, in hyperinfection with pulmonary involvement, larvae can be shown in duodenal biopsy[36]. In disseminated disease, larvae can be found in several extraintestinal sites, such as skin biopsy, cerebrospinal fluid, urine, pericardial, pleural and peritoneal fluid[37–42].

Serological assays are another useful tool in the diagnosis and follow-up of strongyloidiasis. Specific antibodies can be used as a follow-up to prove seroconversion after a successful therapy. There are several commercially available tests with varying sensitivities and specificities. For example, ELISA seems to be a sensitive test (88–95%), albeit with a variable specificity (29–99%)[34]. The low specificity is due to cross-reactivity with other helminth infections, such as filariasis, ascariasis and acute schistosomiasis[34]. However, in Portugal, these are likely not frequent differential diagnosis, and this appear to be a smaller issue with more recent test kits[43]. Another drawback of these tests is their lower sensitivity in severely immunosuppressed patients, and incapacity to accurately distinguish between past and present infection among patients already treated for strongyloidiasis or originating from an endemic country[44]. However, antibody titres tend to diminish with time, although the time required to become negative may be higher than 12 months[5].

Real-time polymerase chain reaction is another tool for the diagnosis of strongyloidiasis, albeit not being readily available in most centres. Estimates of sensitivity of this method are variable but seem high. In the future, molecular testing may enhance the diagnosis of this infection[6,34].

Screening and management

Strongyloidiasis should be a differential diagnosis in any patient with unexplained eosinophilia, especially if there was exposure in endemic areas. However, immunocompetent patients with high risk of exposure should still be screened, even if without eosinophilia[5]. Moreover, in patients with risk factors for developing hyperinfection, testing should also be considered, particularly when having a history of originating or travelling to an endemic country, even if in a distant past[5,11,25]. This is especially important in patients that have immunosuppressive conditions or treatments, such as those with hematologic malignancies, undergoing transplantation or corticosteroid therapy[5]. Indeed, in this case, both parasitological and serological assays should be used[5,25]. In some cases, pre-emptive ivermectin treatment should be considered, if a diagnostic test is not available[5]. However, although corticosteroid exposure has been identified as the main risk factor, there are also reports regarding the use of non-steroid immunosuppressive agents and biologic therapies, including those directed at IL-1, TNFα and lymphocyte depleting drugs[45,46]. Nevertheless, while IgE, IL-13, and IL-4 are paramount for the pathogenesis of this disease, unexpectedly, the modulation of these cytokines has not yet been found to increase risk of strongyloidiasis. Still, pre-treatment screening is advised[47,48]. Additionally, screening should also be considered in those with evidence of HTLV-1 infection[49].

Dermatologists can take advantage of numerous immunosuppressive drugs in the management of several ailments such as chronic immunoinflammatory diseases, psoriasis, and connective tissue disease. It is, therefore, imperative that a screening for the relevant opportunistic diseases be considered prior to the start of treatment. Strongyloidiasis is one such illness, and

several guidelines recommend its screening prior to the start of several medications, primarily corticosteroids[1,2,50]. To do so, likely a combination of serological and microbiological assays is ideal, since in general, serology is highly sensitive, while stool examination is highly specific. Moreover, immunosuppressed patients may have a lower serological sensitivity which might be overcome by an increased detection in stool samples[45,51]. As such, a pre-treatment screen with several (perhaps more than seven) stool samples and serology is advised.

Treatment of strongyloidiasis is usually performed with ivermectin. This broad-spectrum antiparasitic causes muscle paralysis in invertebrates by activating chlorine channels[52]. It is better tolerated and has a similar efficacy than thiabendazole, and is more effective than albendazol[5,25]. In uncomplicated infections a single 200 µg/kg/day oral dose of ivermectin for one or two days usually sufficient[5]. A repetition of this course could be suggested after two weeks, to account for the parasite's autoinfective cycle, however a randomized clinical trial failed to show advantage in this strategy[53].

When considering hyperinfection, there is a lack in high-quality evidence. However, it has been suggested that ivermectin should be given daily or every 48 hours at a dose of 200 µg/kg/day for at least one to two weeks. When the oral route is not well tolerated, alternative routes can be considered. Multiple follow-up stool assessments should be performed, and treatment continuation until no more larvae are found in faeces should be considered[7,25]. Additionally, whenever iatrogenic immunosuppression is present, reduction in these regimens should be considered, when clinically feasible[25]. Moreover, these patients should be considered infectious and put under standard contact precautions[49].

The high mortality in hyperinfection is often due to a lack of awareness in the need for parasite screening before the start of corticosteroid therapy[28]. Indeed, several patients with fatal outcomes after treatment with empirical corticosteroids are later confirmed as a case of disseminated strongyloidiasis. Moreover, the possibility of infection with this nematode should be considered in any immunocompromised patient who suddenly deteriorates without any apparent cause, since delay in treatment often results in death[14].

Conclusion

Currently, strongyloidiasis is a rare disease in Portugal, mostly related to migrant population. However, it can have a severe if not fatal course, especially amongst immunosuppressed patients. As such, and since chronic infection can often be asymptomatic, screening prior to the start of immunosuppressive treatment (especially corticosteroids) is imperative. Dermatologists that prescribe such regimens should be familiar with the need of parasite screening and management prior to the start of therapy.

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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Port J Dermatol and Venereol. **CASE REPORT**

Syphilitic hepatitis: a rare complication of secondary syphilis. A case report

Hepatite sifilítica: uma complicação rara da sífilis secundária. O reporte de um caso

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Abstract

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*, progressing through active and latent stages if left untreated. Hepatic involvement can occur in secondary syphilis, but this is an uncommon complication, with few published case reports. A 34-year-old man without significant medical history was admitted to the gastroenterology department with a 2-week history of unexplained jaundice and acute cholestatic hepatitis. He also presented with erythematous papules and plaques in the genital area, suggestive of secondary syphilis. *T. pallidum* hemaglutination assay and venereal disease research laboratory test were both positive, the latter with a 1:16 titer. The diagnosis of secondary syphilis with hepatic involvement was considered. The improvement of cutaneous and laboratory findings after intramuscular benzathine penicillin injection supported this hypothesis. Symptomatic cholestatic hepatitis is a rare feature of the systemic spectrum of secondary syphilis. The clinical and laboratorial response after penicillin treatment is a strong clue for this diagnosis.

Keywords: Syphilis. Hepatitis. *Treponema pallidum*. Case report.

Resumo

A sífilis é uma patologia de transmissão sexual causada pelo *Treponema pallidum* que, quando não tratada, evolui por períodos de atividade e latência. O envolvimento hepático pode ocorrer na sífilis secundária, sendo uma complicação rara, com poucos casos publicados. Um homem de 34 anos, previamente saudável, encontrava-se internado no serviço de Gastroenterologia para investigação de icterícia, hepatite e colestase inexplicadas, com cerca de 2 semanas de evolução. Adicionalmente, tinha placas eritemato-descamativas localizadas no pénis. A pesquisa de testes treponémicos e não-treponémicos foi positiva, pelo que se colocou a hipótese diagnóstica de sífilis secundária com envolvimento hepático. O tratamento com injeção intramuscular de penicilina benzatínica em dose única com subsequente melhoria dos achados cutâneos e laboratoriais corroborou a hipótese prévia. A hepatite sifilítica pode fazer parte do espectro da sífilis secundária. A melhoria clínica e laboratorial após o tratamento com penicilina é uma pista forte para este diagnóstico.

***Palavras-chave*:** Sífilis. Hepatite. *Treponema pallidum*. Case report.

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What does this study add

We present an uncommon complication of secondary syphilis. Our goal is to raise awareness for this complication, so it's included in the investigation of otherwise unexplained hepatitis and to search for hepatic alterations in patients diagnosed with syphilis.

Introduction

Syphilis, the infection caused by the spirochete *Treponema pallidum*, is a sexually and, less frequently, vertically transmitted disease. The untreated condition is polymorphic, progressing through active stages and latency. Early syphilis is contagious and occurs in the first 2 years of the infection, including primary, secondary, and early latent syphilis. Late syphilis (late latent and tertiary syphilis) is not contagious and has subtler manifestations[1].

The primary lesion develops at the inoculation site as a firm, painless, ulcerated papule that spontaneously resolves. It is followed by dissemination and multiplication of the spirochete in several organs, a stage known as secondary syphilis. This is characterized by a broad spectrum of manifestations involving not only the skin, but also several internal organs. A latent phase follows, which is asymptomatic and can last for several years. Tertiary syphilis is rare nowadays, with severe involvement of several systems, such as the skin, bones, central nervous system, and heart[1]. Symptoms can be subtle and unspecific, a feature that has led to the historical denomination of "the great imitator".

Hepatic disease is a possible but uncommon complication in the systemic spectrum of secondary syphilis[2], feasibly caused by non-hepatotropic involvement of the liver by the bacteria[3]. There are less than 150 cases of this complication described until 2018[4]. Herein, we present the case of a young adult man with syphilitic hepatitis.

Case presentation

A 34-year-old man presented to the emergency department with jaundice, malaise, and fatigue. He was otherwise healthy, with no history of new medications, recreational drugs, or alcohol consumption. He denied fever, abdominal pain, or anorexia. Laboratorial investigation revealed hyperbilirubinemia, elevated liver enzymes, and cholestasis (Table 1). Serologies for hepatitis viruses and human immunodeficiency virus were negative. He was admitted for further diagnostic investigation and monitoring.

Dermatology was consulted regarding asymptomatic cutaneous lesions in the genital area with similar duration as the remaining symptoms. The patient had sexual intercourse exclusively with women (two different partners in the previous 6 months) and no history of previous sexually transmitted diseases was found. He denied genital or oral ulcers in the preceding months. There was no personal or family history of skin diseases. Examination disclosed psoriasiform erythematous and desquamative plaques and papules in the penis, with round shape and well-defined borders (Fig. 1), suggestive of secondary syphilis. A left inguinal adenopathy was palpable. Further laboratorial investigation revealed positive *Treponema pallidum* hemaglutination assay and Venereal Disease Research Laboratory, the latter with a 1:16 titer, supporting the clinical diagnosis. The diagnosis of secondary syphilis with probable hepatic involvement was considered and treatment with a single injection of intramuscular benzathine penicillin at dose of 2.4 million units was performed. Bilirubin, liver enzymes and cholestasis parameters progressively decreased following treatment (Table 1). Progressive improvement of jaundice and genital lesions was simultaneously observed.

Additional laboratorial investigation was negative for hepatitis A, B, C, and E virus, cytomegalovirus, Epstein-Barr virus, and liver autoantibodies. Imaging studies, including abdominal ultrasonography and magnetic resonance cholangiopancreatography, were unremarkable. Liver biopsy was unspecific, with maintained hepatic architecture and mild inflammatory portal infiltration, with negative immunohistochemical staining for *T. pallidum*.

The patient was discharged 9 days after treatment, completely asymptomatic. He was referred to a Gastroenterology and Dermatovenereology outpatient clinic and had complete response to therapy, achieving a fully resolution of hepatic and skin alterations. The patient missed subsequent evaluations and was lost to follow-up.

Discussion

Liver damage in luetic infection occurs most frequently in early syphilis, particularly in secondary stage[4], and syphilitic hepatitis is thought to occur in 0.2 - 2.7% of patients with secondary syphilis[4-6]. Mullick[6] proposed four diagnostic criteria for syphilitic hepatitis in 2004: (1) abnormal liver enzyme levels; (2) serological evidence for syphilis in conjunction with an acute clinical

Table 1. Values of liver enzymes before and after penicillin treatment

	Normal values	At admission	10 days after treatment
Total bilirubin (mg/dL)	< 1.20	12.84	3.52
Direct bilirubin (mg/dL)	< 0.50	9.29	2.49
AST (U/L)	< 34	254	84
ALT (U/L)	< 55	354	158
GGT (U/L)	< 64	1385	468
ALP (U/L)	< 150	1408	704

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase.

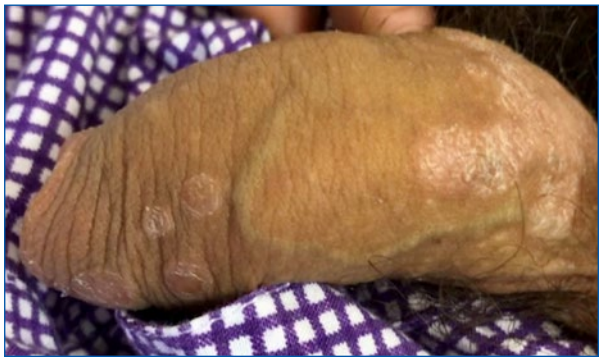

Figure 1. Penile erythematous and desquamative plaques and papules, with round shape and well-defined borders, disclosing a psoriasiform appearance.

presentation consistent with secondary syphilis; (3) exclusion of alternative causes of hepatic damage; and (4) improvements in liver enzyme levels after penicillin therapy. The presented case fulfilled all these criteria.

The pathogenesis of luetic hepatitis is still largely undetermined, but direct portal venous inoculation and immune-complex formation have been suggested[7]. However, given the paucity of spirochete direct recognition in the liver, direct hepatotoxicity induced by the bacteria is unlikely[8,9].

Homosexual men in the fourth to fifth decades of life seem to be affected more often, in particular if infected with HIV[4]. The most frequent clinical findings include skin rash, anorexia, jaundice, and fever[4]. Laboratorial investigation exhibits a substantial increase in cholestasis parameters, like alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT), with mild elevations in aminotransferases and total bilirubin[4]. Histologic features of syphilitic hepatitis include bile duct inflammatory infiltration, which correlates with ALP and GGT levels[4]. Spirochete identification with immunohistochemical staining is rare[4], as in our case. Liver biopsy was performed in this patient as a part of the diagnostic approach of unexplained hepatitis, before the diagnosis of syphilitic involvement was made.

Penicillin remains the first treatment line, and the subsequent decrease of liver enzymes is one of the diagnostic criteria of syphilitic hepatitis[6]. Our patient was treated with the standard dose for secondary syphilis, and no iatrogenic reactions were observed.

Conclusion

The discrepancy between the estimated occurrence of syphilitic hepatitis and the number of published cases suggests that this condition is probably overlooked. The present case raises awareness for this complication, that should be included in the differential diagnosis of sexually active patients with abnormal liver enzymes of no obvious cause.

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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CASE REPORT

Pediatric ashy dermatosis: what to expect?

Dermatose cinzenta pediátrica: o que esperar?

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Abstract

Ashy dermatosis is a pigmentation dermatosis that belongs to the group of acquired macular hyperpigmentation disorders of uncertain etiology. Although the adulthood forms usually occur in higher Fitzpatrick skin types, pediatric cases are more common in lower phototypes. The authors report two cases of pre-pubertal ashy dermatosis and perform a brief review of literature to highlight the differences in epidemiology and course of the disease in children and adults.

Keywords: Ashy dermatosis. Erythema dyschromicum perstans. Pigmentation. Dermis.

Resumo

A dermatose cinzenta é uma doença da pigmentação que pertence ao grupo dos distúrbios de hiperpigmentação macular adquirida de etiologia incerta. Embora as formas do adulto ocorram habitualmente em fotótipos cutâneos de Fitzpatrick elevados, os casos pediátricos são mais comuns em fotótipos baixos. Os autores reportam dois casos de dermatose cinzenta em idade pediátrica e descrevem uma breve revisão da literatura para salientar as diferenças de epidemiologia e de curso da doença em crianças e adultos.

***Palavras-chave*:** Dermatose cinzenta. Eritema discrómico perstans. Pigmentação. Derme.

Introduction

Ashy dermatosis (AD) is a pigmentation dermatosis that belongs to the group of acquired macular hyperpigmentation disorders of uncertain etiology. It presents with blue-gray macules, symmetrically located on the trunk, neck and upper extremities[1]. Although the adulthood form is more common in higher Fitzpatrick skin types, pediatric cases are more common in Caucasian individuals with lower phototypes[1]. The authors report two cases of AD in pre-pubertal age and highlight the differences in epidemiology and course of the AD in children in comparison with adults.

Case report 1

An 11-year-old boy, Fitzpatrick skin type III, presented with multiple blue to gray oval macules and patches

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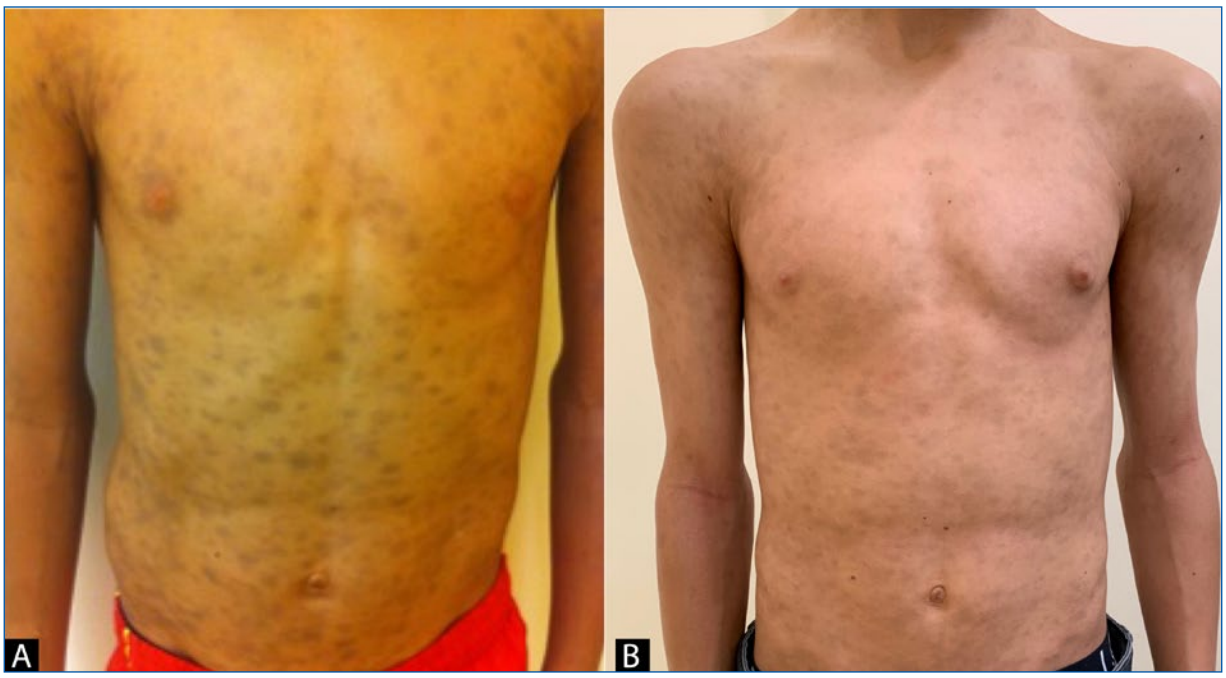

Figure 1. **A:** patient 1 at the first visit. **B:** patient 3 years of follow-up.

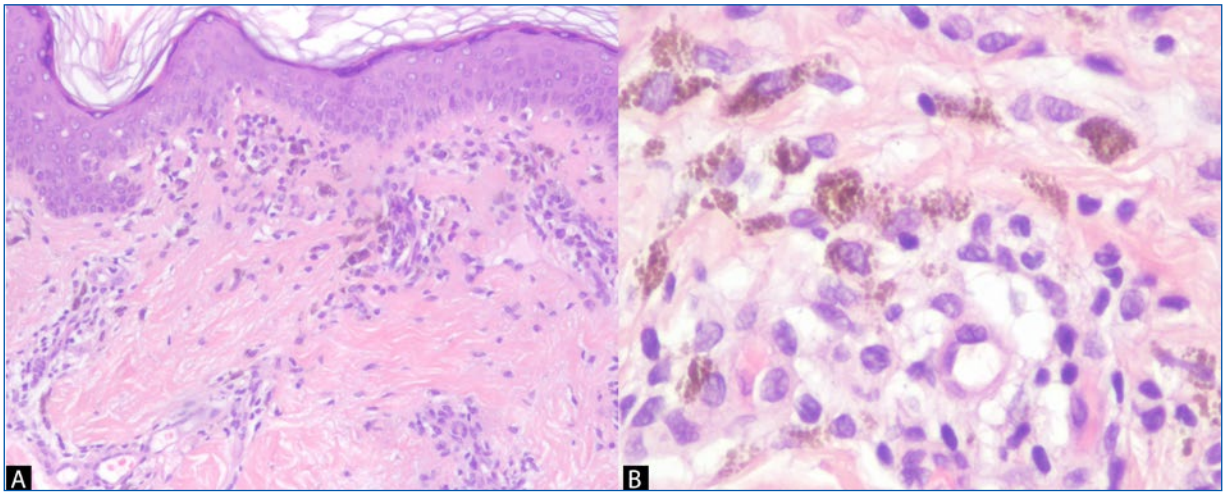

Figure 2. Histopathology of patient 1 with focal vacuolar changes in basal stratum of epidermis, mild inflammatory perivascular infiltrate, dehiscence of pigment with interstitial and perivascular melanophages (**A**: H&E, x100; **B**: H&E, x400).

between 5 and 15 mm, on his trunk, neck and proximal thighs (Fig. 1A). No erythematous border of the lesions was observed. The lesions had appeared suddenly one month before the dermatological observation and were asymptomatic. He was otherwise healthy and there was no previous intake of medication. His twin brother had no similar lesions. He was sent to the Dermatology Department with a diagnosis of multiple ecchymoses. His complete blood count and coagulation times were within the normal range. There was no history of trauma. A skin biopsy was performed and histopathology revealed focal vacuolar changes in basal stratum of the epidermis, a mild inflammatory perivascular infiltrate and dehiscence of pigment with interstitial and perivascular melanophages (Fig. 2).

A diagnosis of AD was made. The boy started treatment with a mometasone furoate 0.1% cream for 4 weeks, with no improvement of the dermatosis. At 3 years' follow-up, lesions remain unchanged (Fig. 1B).

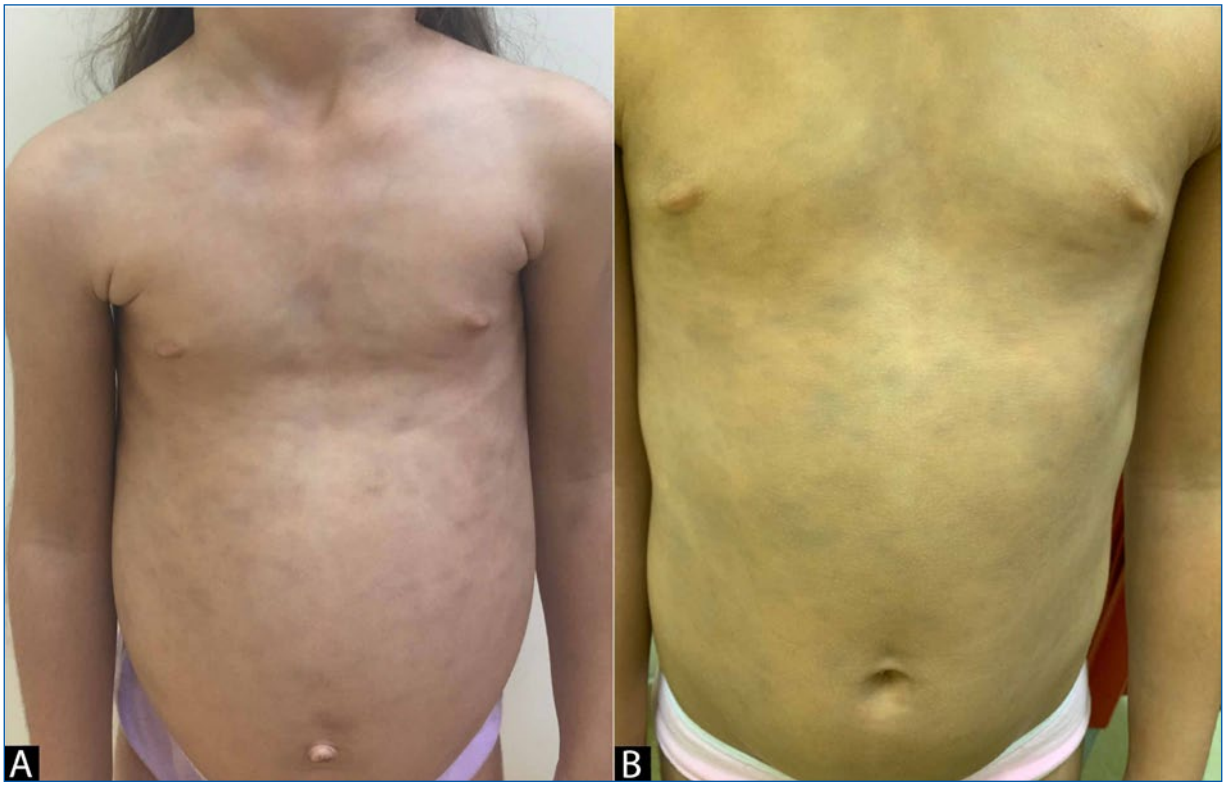

Figure 3. **A:** patient 1 at the first visit. **B:** patient 2 years of follow-up.

Case report 2

A 5-year-old girl, Fitzpatrick skin type II, presented with 5-20 mm, grayish oval macules on her trunk (Fig. 3A) with no erythematous rim. The lesions had had a gradual onset for 2 months. At the same time, the girl developed abdominal pain with diarrhea which led to the diagnosis of celiac disease. A biopsy of a cutaneous lesion revealed abundant perivascular macrophages with intracytoplasmic brownish pigment and no epidermal changes (Fig. 4).

With a diagnosis of AD and celiac disease, the child started a gluten free diet with improvement of the gastrointestinal symptoms but no improvement of cutaneous lesions. No topical or systemic treatment was attempted. At 2 years' follow-up, she maintains the same lesions (Fig. 3B).

Discussion

Ashy Dermatosis (AD) was first described in individuals from El Salvador in 1957[2]. AD patients experience an onset of bluish or grayish macules, sometimes with an erythematous and elevated rim which eventually disappears within several months. Trunk, neck and upper limbs are the most commonly involved areas followed by face and lower limbs[1,3]. Palms and soles are usually unaffected[4,5]. Although it usually spares the mucous membranes, lesions on the oral cavity have been reported[6]. In most cases this is an asymptomatic condition but some patients may refer mild pruritus[4].

Many authors consider AD and erythema dyschromicum perstans (EDP) as the same disorder. However, a consensus published by a group of pigmentary disorders experts consider these as two separate entities, with the major difference between them being the presence of an erythematous border in the early active phase of EDP[2]. If there is no history or active presence of the erythematous border, it should be considered as AD[1,2]. Chang et al. reported that only 17.6% of 68 Korean patients with AD/EDP presented with the erythematous raised border[3].

There are some interesting differences between childhood and adulthood cases. While most adult patients are Hispanic with higher phototypes, children affected are usually Caucasian and have lower phototypes[4,7]. Another difference is the spontaneous improvement or resolution in 50-69% of pre-pubertal patients,

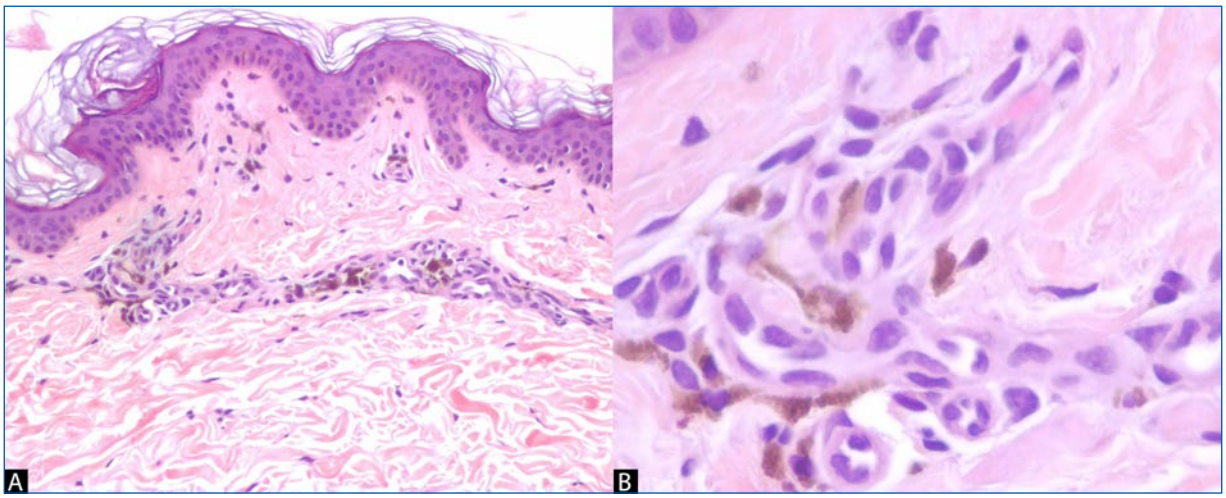

Figure 4: Histopathology of patient 2 with abundant perivascular macrophages with intracytoplasmic brownish pigment (**A:** H&E, x100; **B:** H&E, x400).

which contrasts with the persistent course in adults[2,7]. However, the evidence regarding pediatric patients is still limited, as few reports have addressed this dermatosis in children[4,7].

Although there were some reports of AD following drugs and infections, the etiology mostly remains unknown[2,3,7,8]. In our patients, no clear trigger was identified except for the almost simultaneous onset of celiac disease on the second patient. However, we could not make a clear relation between these two entities as the gluten-free diet improved celiac disease manifestations but did not affect AD. A genetic contribution has also been proposed to contribute to the development of the AD[2]. However this could not be supported by our cases, since the first patient had a twin brother without lesions.

Primary histopathologic findings include pigment incontinence and melanophages in the dermis, along with mild to moderate superficial perivascular lymphocytic infiltration. Usually there is basal vacuolar degeneration and a focal or lichenoid pattern with colloid bodies along the dermoepidermal junction [1,4].

Basal vacuolar degeneration and edematous papillary dermis with lymphocytic infiltrate indicate active lesions, whereas inactive lesions show melanophages and pigment incontinence in the dermis, with no inflammation[3]. This is in accordance with both our cases. In case 1, which presented to our department few weeks after the onset of the dermatosis, we found vacuolar alterations in the basal layer, with a mononuclear infiltrate, suggesting an active phase. In case 2, we did not find these aspects typical of the active phase, which is compatible with the longer duration of the dermatosis of the child before presenting to our consultation. However, the lack of the lichenoid aspects in case 2 makes it difficult to assume a definitive diagnosis of AD over idiopathic eruptive macular pigmentation (IEMP).

Other conditions may mimic AD/EDP, such as lichen planus pigmentosus (LPP) and IEMP.

Lichen planus pigmentosus (LPP) most frequently affects sun-exposed areas, such as the face and neck, but can also affect flexural folds and rarely the oral mucosa[1,9]. While AD typically has a stable course, LPP is more likely to have a wax and waning history[9]. Histopathology alone cannot differentiate between AD/EDP and LPP[10]. Dermoscopy has been described as a useful tool when in doubt with LPP. In AD, dermoscopy shows gray-bluish small dots over a bluish background, whereas in LPP dots are brownish and larger than AD dots, and occur over a brownish background[11].

Idiopathic eruptive macular pigmentation (IEMP) is an eruption of asymptomatic brownish macules, affecting the trunk, neck and proximal extremities, with no previous inflammatory lesions or drug exposure[1]. Lesions are typically smaller than the ones observed in AD[2]. IEMP affects both dark and light phototypes[1]. There is usually a hyperpigmentation of the basal layer of epidermis and prominent dermal melanophages, with no basal layer damage or lichenoid inflammatory infiltrate[2,10]. Lesions resolve without treatment in several months to years[1].

There is no uniformly effective therapy for AD/EDP[2], and most evidence regarding treatment results from case reports in adults. Although topical steroids are the most commonly used agents[3,5], other options such as

topical hydroquinone[3,9], topical calcineurin inhibitors[5,12] and topical tretinoin[3,9] have been described with variable outcomes. Numata et al. reported the disappearance of the erythematous halo of the EDP lesions in an adult after the use of a topical steroid, but pigmented macules and patches persisted[13]. Multiple systemic drugs have been tried in the treatment of AD/EDP in adults, such as isotretinoin[14,15], minocycline[3], clofazimine[16], dapsone[5,17], and oral steroids[9,15]. There is also a report of resolution of AD after the administration of pembrolizumab in a 62-year-old patient with squamous cell carcinoma of the lung[18]. Phototherapy with narrow band UVB has been successful in the treatment of a 17-year-old male[19].

In both cases reported in this article, no systemic treatment was attempted due to the benign course of the disease and lack of and lack of an effective and safe medication available. Spontaneous improvement or resolution of the lesions is seen in the majority of pre-pubertal children[2,4]. In a cohort of patients observed between 3 and 76 years, complete clearing was reported in 2%, improvement in 43.1%, worsening in 5.9%, and 49.0% showed no significant change[3]. Silverberg et al. reported complete clearance of AD in 5 of 8 pre-pubertal patients, with an average clearance time of 2.5 years and the longest duration of 5 years. The remaining three patients missed the follow-up[7].

Conclusion

AD is a benign condition observed more common in Hispanic adult patients. However, considering the pre-pubertal age, it is more frequently observed in Caucasian children. Its insidious and persistent course may alarm the child's caregivers. Therefore, it is important to explain them that although no efficient and safe therapy exists, most children will progress towards a spontaneous improvement or resolution.

Presentations

Part of the current work has been presented at the Spring Meeting of the Portuguese Society of Dermatology and Venereology, in May 25, 2019, Curia, Portugal.

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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CASE REPORT

Cutaneous ectopic schistosomiasis associated with Löffler syndrome. A rare case report

Esquistossomose ectópica cutânea associada a síndrome de Löffler. Um raro relato de caso

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Abstract

Schistosomiasis mansoni is an endemic disease in Brazil, usually causing systemic symptoms, mainly gastrointestinal. Skin lesions are best described in the acute phase of the infection, with ectopic skin lesions rarely seen. We report a case of schistosomiasis with rare ectopic cutaneous involvement, with perianal papules and plaques, acquired in the state of São Paulo in 2020. At the beginning of the investigation, the hypothesis of infection by COVID-19 was raised, due to a pulmonary condition, but it was discarded after a negative PCR for the virus. Due to eosinophilia, pulmonary CT characteristics and epidemiology, Löffler's syndrome was suspected. The definitive diagnosis of schistosomiasis was given, after the onset of the skin rash, by the anatomopathological examination of the skin biopsy, thus avoiding an invasive examination—lung biopsy, in the patient who was using anticoagulants. The protoparasitological examination of faeces was negative. The patient was treated with Praziquantel, with the improvement of the condition. This report demonstrates the importance of dermatological examination and skin biopsy for the definitive diagnosis of Schistosomiasis in a patient with severe systemic manifestations.

Keywords: Cutaneous schistosomiasis. Schistosomiasis mansoni. Neglected diseases. Parasitic diseases. Loffler syndrome.

Resumo

A esquistossomose mansônica é uma doença endêmica no Brasil, causando geralmente sintomas sistêmicos, principalmente gastrointestinais. As lesões cutâneas na doença são melhores descritas na fase aguda da infecção, sendo que lesões cutâneas ectópicas são raramente vistas. Relata-se o caso de esquistossomose com acometimento cutâneo ectópico raro, localizado à região perianal e glútea, adquirido no estado de São Paulo em 2020. No início da investigação diagnóstica fora aventada hipótese de infecção por COVID-19, devido quadro pulmonar, mas esta foi descartada após PCR negativo para o vírus. Em decorrência da eosinofilia, características da TC pulmonar e epidemiologia suspeitou-se de síndrome de Löffler. O diagnóstico definitivo de esquistossomose foi dado, após início do quadro cutâneo, pelo exame anatomopatológico da biopsia

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da lesão, evitando assim um exame invasivo - biópsia pulmonar, no paciente que estava em uso de anticoagulantes. O exame protoparasitológico de fezes foi negativo. O paciente foi tratado com praziquantel, evoluindo com melhora do quadro. Este relato demonstra a importância do exame dermatológico e da biópsia de pele para o diagnóstico definitivo num paciente com manifestações sistêmicas graves.

Palavras-chave: Esquistossomose cutânea. Esquistossomose mansoni. Doenças negligenciadas. parasitose. Síndrome de Loffler.

Introduction

Schistosomiasis mansoni is a systemic disease caused by a trematode helminthic which represents a public health problem in Brazil and in the world[1].

Skin lesions are observed mostly in the acute phase (swimmer`s itch or cercarial dermatitis), and are very unusual in the chronic forms of schistosomiasis, even in endemic areas[2].

The cutaneous form is usually asymptomatic, and it occurs often in white young women. Chronic lesions are formed when the eggs or worms migrate to the skin, causing granulomas on the skin and mucous membranes[3,4].

We report the case of a male patient, who after a trip to the coast of São Paulo, developed the systemic schistosomiasis that was correctly diagnosed only after skin biopsy.

Case report

A previously healthy male patient–D.G.D., aged 17-year-old, used to swim in river waters on family trips. One month after his trip to "Juréia" and "Boracéia," in the South Coast of São Paulo state, in February 2020, he developed fever, dry cough, and diarrhea, progressing with prostration and desaturation, requiring hospital admission and additional oxigenotherapy. With the hypothesis of viral infection (COVID-19 or Influenza), he was medicated with Oseltamivir and Amoxicillin Clavulanate, but PCR for COVID-19 and Influenza were negative.

A computed tomography (CT) of the thorax revealed multiple solid sparse nodules distributed bilaterally on the lung parenchyma, some of them with halo in opaque glass, measuring up to 10 mm, and additional splenomegaly. Laboratory examinations showed leucocytosis (15.090/mm^3) with 38.2% eosinophils (5.760/mm^3). A protoparasitological examination of feces was negative. Pneumonology suspected of Löffler`s Syndrome, and prescribed Ivermectin 18 mg/day for 2 days and Albendozole 400 mg/day for 6 days, aiming to treat *Ascaris lumbricoides* or *Strongyloides stercoralis*. Nevertheless, one day after onset of this treatment, he developed a cutaneous rash on the dorsum, axillae and inguinal region (Fig. 1), suggesting possible toxemia secondary to antigen release from the dead helminths. Hydrocortisone 100 mg every 12 hours was soon initiated with improvement of the rash in a few days.

However, just 2 days after stopping Ivermectin, the patient developed symmetrical erythematous papular lesions, some isolated and with minor excoriations and others confluent into small plaques, localized on the buttocks and perianal area (Fig. 2). A skin biopsy of the right buttock demonstrated eosinophilic granulomas associated with typical parasitic eggs (Fig. 3), confirming the diagnosis of Schistosomiasis. Also indirect immunofluorescence assay to *S. mansoni* was positive 1/64. Treatment with praziquantel, 4.2 g as a single dose induced total relief, improving his clinical status after 1 week, including complete resolution of perianal cutaneous lesions.

Discussion

Schistosomiasis is still a serious health problem in Brazil[6], with *S. mansoni* as the only species found in this country[8]. It is acquired in contact with contaminated water, and transmission depends on snails of the genus Biomphalaria, found in freshwater-bathed regions[7]. When carrying out their domestic and leisure activities in rivers, lakes and ponds, humans are exposed to the larva, that have left the snails, which actively penetrate the skin and mucous membranes[7]. The larvae reach the blood vessels and portal circulation, where they will become adult worms[8].

Soon, after the infective contact, cercarial dermatitis may occur, which presents with pruritus, usually transient, and an erythematous micropapular eruption. After about 40-60 days, coincident with the laying of eggs[6], usually in the mucosa and submucosa of the colon and rectum veins[9], patients develop high fever, chills, sweating, malaise and asthenia, followed by diarrhea, nausea, and vomiting, which constitute the phase entitled Katayama fever. Associated

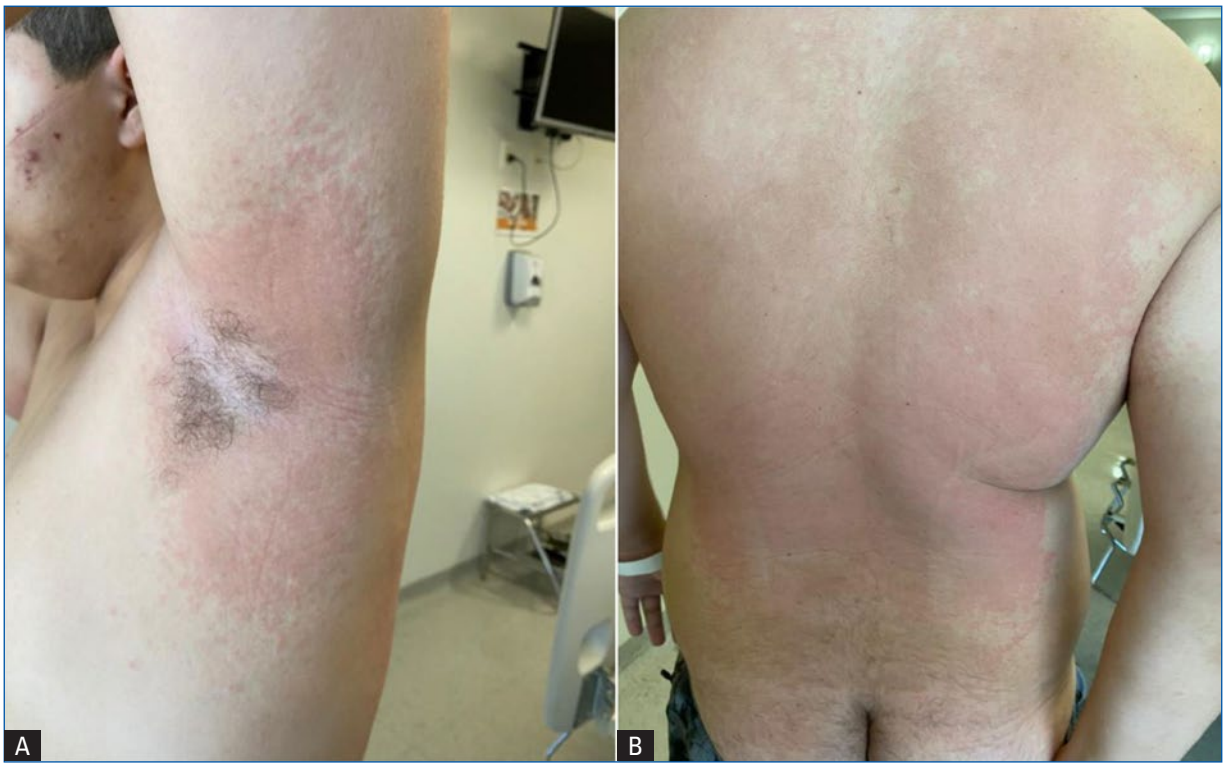

Figure 1. A and B: maculopapular exanthema with predominant involvement of the axillae (**A**), inguinal region and dorsum (**B**), which developed within 24hours on onset of Albendazole and Ivermectin.

hepatosplenomegaly and significant eosinophilia, often lead to the diagnosis of acute schistosomiasis[7]. In its chronic phase that occurs more than 6 months after infection various organs may be affected with signs and symptoms of intestinal, hepato-intestinal or hepatosplenic involvement, as well as neurological and cutaneous forms[7,8]. Tissue granulomas may form in response to the presence of the eggs, classically leading to bowel wall thickening, periportal fibrosis of the liver and portal or pulmonary hypertension[10].

Pulmonary involvement can be divided into two vascular clinical forms: hypertensive and cyanotic. The first is characterized by dyspnea on exertion, palpitations, dry cough, and constrictive chest pain, which can also lead to extreme asthenia and fatigue, in addition to heart failure. The cyanotic form has a worse prognosis and presents with generally mild cyanosis, especially in the extremities[6]. Pulmonary manifestations can also occur during the migration of larval forms, such as the so-called Loffler syndrome, manifesting with dyspnea and dry cough and characterized by accumulation of eosinophils in the lungs[10], which is consistent with the initial presentation of the present case that did not show the typical signs of Katayama fever.

Skin lesions of chronic schistosomiasis are generally characterized as papular, ulcerative, granulomatous, and fistulous lesions, often affecting the skin of the genital and perianal region, secondary to the deposition of eggs contiguous to the pelvic vessels[9]. Infiltrative lesions in these regions can cause an inflammatory and fibrotic reaction, leading to the formation of granulomas that begin as asymptomatic firm papules that grow slowly, until they become vegetative[8]. In rare circumstances, the eggs are lodged in extragenital skin, causing cutaneous ectopic schistosomiasis[9], and lesions may be found on the back and abdomen. The exact mechanism of egg deposition in the skin remains unknown, suggesting that anastomoses between venous systems would be associated with the migration of eggs or adult worms to ectopic sites[8].

Diagnosis is based on characteristic lesions, compatible epidemiology and histopathological examination[3]. Histopathology provides identification of *S. mansoni* eggs, surrounded by inflammatory cells, mainly lymphocytes and eosinophils in more recent lesions, but in old lesions necrosis and granulomatous infiltrates predominate[2,10]. The coprologic examination can be used preferably with the use of quantitative

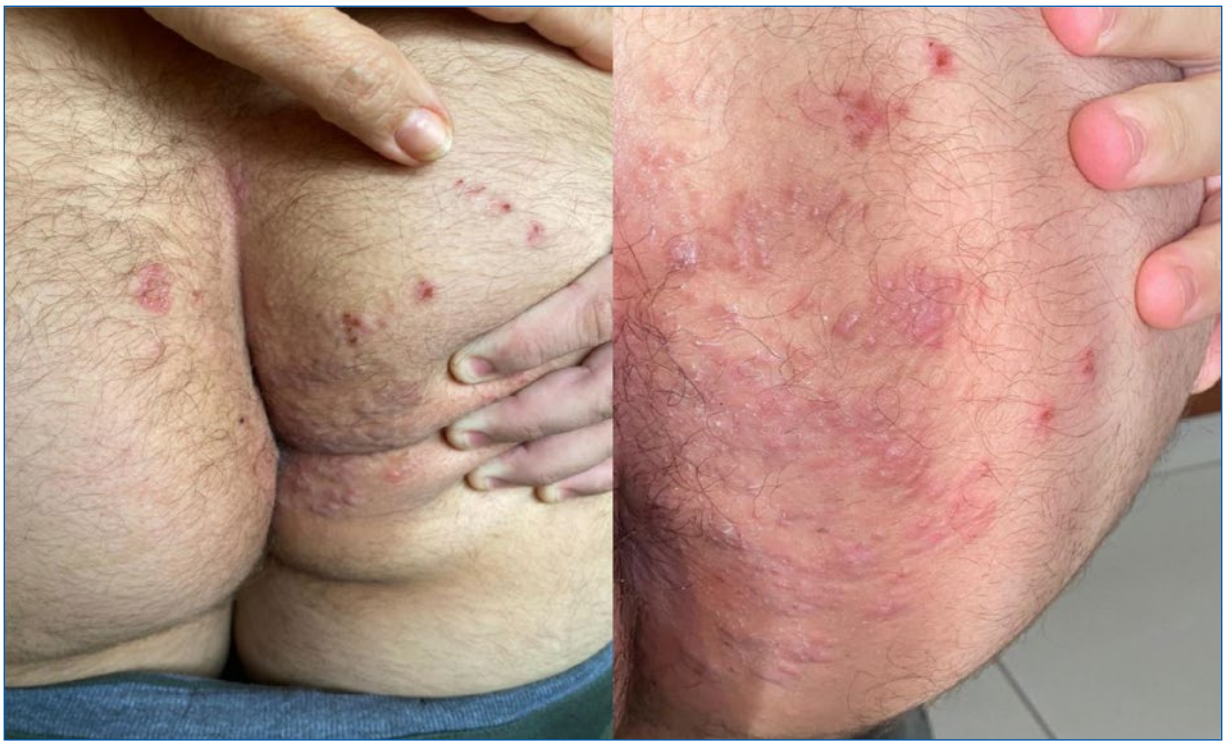

Figure 2. Erythematous papules some isolated, others grouped in small plaques, others ulcerated on the buttocks.

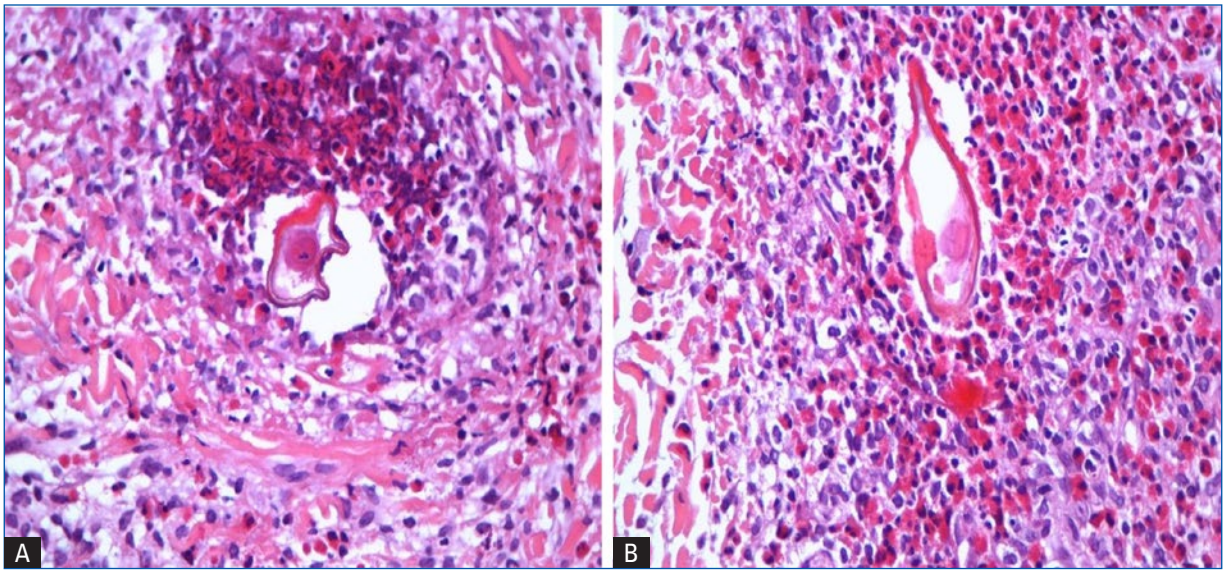

Figure 3. A and B: Histopathological images of the skin biopsy, showing of typical egg of Schistosoma mansoni, surrounded by a granulomatous reaction very rich in eosinophils (H&E–300x).

and sedimentation techniques[4]. Diagnosis can also be confirmed by combining the results of an indirect hemagglutination assay and enzyme-linked immunosorbent assay test, which reach a sensitivity and specificity beyond 90 and 97% respectively[5]. As in our case significant eosinophilia is very frequent. Meltzer et al. described that 53.7% if patients with significant eosinophilia after a trip were diagnosed with schistosomiasis. Around 47.7% of the patients suffered from schistosomiasis acute crisis, 16.9% patients presented chronic symptoms and 36.6% were asymptomatic[5].

The gold standard treatment is praziquantel 60 mg/kg for children until 15 years old and 50 mg/kg for adults, in a single dose with high healing rates (60-90% in endemic areas and about 100% in non-endemic areas)[2,10]. The second-choice drug is the oxamniquine 15 mg/kg, a single dose in adults, and 20 mg/kg, as single dose on children up to 15 years old.

What does this study add to the current knowledge?

This study approaches a rare case of cutaneous schistosomiasis with Löffer syndrome, a rare presentation, despite being an endemic disease in Brazil. We`ve alerted to the necessity for the accurate diagnosis, which in this case was based on the skin biopsy.

Acknowledgments

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Ethical considerations

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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CASE REPORT

Sirolimus in the treatment of cystic lymphangioma in a pediatric patient

Sirolimus no tratamento de um linfangioma quístico num doente pediátrico

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Abstract

Cystic lymphangioma (CL) is a rare benign tumor, which occurs typically during childhood, with craniofacial, cervical or axillary being the most common locations. Lymphangiomas management can be challenging due to their permeative growth throughout tissue layers. Sirolimus is an immunosuppressive and antitumor agent that can inhibit abnormal vascular proliferation by blocking the mTOR/PI3K pathway. It is typically well-tolerated, with nausea, cytopenias, and metabolic imbalances as the most significant adverse effects. We present the case of a pediatric patient in which sirolimus was used to treat a macrocytic lymphangioma, highlighting its effectiveness and safety.

Keywords: Lymphangioma. Sirolimus. Pediatrics.

Resumo

Os Linfangiomas Quísticos são tumores benignos raros, que ocorrem tipicamente na infância e se localizam mais frequentemente nas regiões craniofacial, cervical ou axilar. Dada a sua natureza infiltrativa em todas as camadas de tecido, o tratamento dos linfangiomas torna-se desafiante. O Sirolimus é um agente imunossupressor e antitumoral que inibe a proliferação vascular anormal ao bloquear a via de sinalização mTOR/PI3K. Geralmente é bem tolerado, tendo como efeitos adversos mais significativos náusea, citopenias e desequilíbrios metabólicos. Descrevemos o caso de uma criança em que foi usado sirolimus no tratamento de um linfangioma macroquístico, demonstranto a sua eficácia e segurança.

Palavras-chave: Linfangioma. Sirolimus. Pediatria.

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Introduction

Cystic lymphangioma (CL) is a rare benign tumor resulting from a failure in the development of the lymphatic system, which occurs more typically during childhood[1]. They consist of dilated lymphatic channels forming multiple cysts of variable size (macro- or microcystic lymphangioma), with craniofacial, cervical, or axillary being the most common locations[1,2]. Surgical excision has been historically considered the treatment of choice, but today less invasive therapeutic options are preferred[2].

Sirolimus is an antitumor agent that belongs to the mammalian target of rapamycin (mTOR) inhibitors group, it blocks the mTOR/PI3K pathway and reduces the production of vascular endothelial growth factor (VEGF) and responsiveness of its receptors, thus inhibiting abnormal vascular proliferation. Sirolimus and other mTOR inhibitors are predicted to be effective agents in disorders in which the mTOR growth control pathway is affected[2,3].

We present the case of a 3-year-old boy treated with oral sirolimus for a cervical CL.

Case description

A 3-year-old, previously healthy boy was referred to the pediatric outpatient clinic due to a right cervical mass, first noticed at the age of 17 months.

Physical examination was remarkable for a voluminous cervical mass on the right side, with approximately 6 cm (Fig. 1) with no other significant findings.

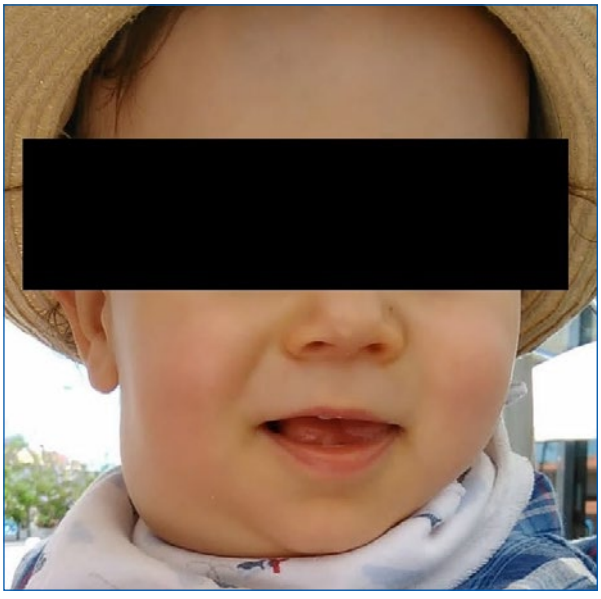

Figure 1. A voluminous cervical mass at the age of 3 years, before treatment.

The ultrasound of the mass revealed a cystic multiloculated image, with anechogenic content measuring 77.7 x 65 x 29 mm and permeating through the cervical structures, below the parotid, posteriorly to the submandibular gland and around the jugulo-carotid space. Magnetic resonance imaging (MRI) confirmed the existence of a right cervical mass consistent with a CL with 6.7 x 6 x 5.2 cm (Fig. 2).

Treatment with sirolimus was started at 1 mg/m^2/dose twice daily. Regular monitoring was carried out with no adverse effects reported.

After 1 year and 3 months of treatment, an important reduction of the mass was achieved (Figs. 3A and B). An MRI showed a significant reduction of the right cervical CL (40 x 28 x 40 mm (Figs. 4A and B).

The patient maintains treatment with sirolimus after 2 years and 3 months with no side effects, and clinically he has no visible mass (Figs. 3C and D).

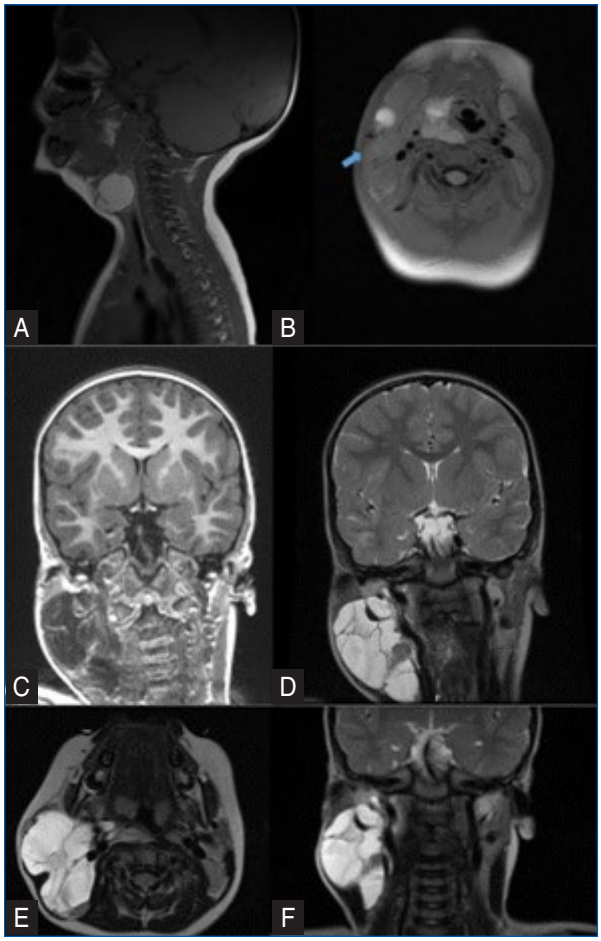

Figure 2. A and B-top: MRI images of the lymphangioma at the date of diagnosis. **Bottom-C, D, E, and F:** immediately before treatment with sirolimus was started.

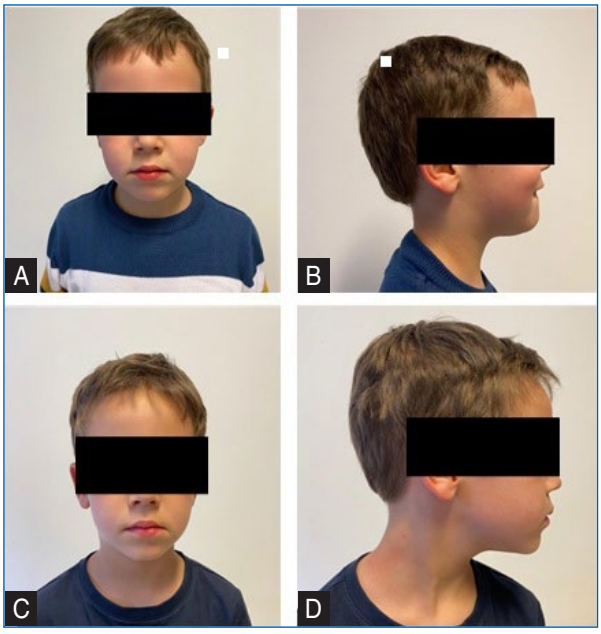

Figure 3. **A and B:** picture of the patients after 1 year. **C and D:** 2 years of treatment with sirolimus, both with no visible mass.

Discussion

It has been suggested that both the occurrence and development of CLs are caused by somatic activating mutations in PIK3CA. This mutation leads to an abnormal activation of the phosphatidylinositol-3′-kinase (PI3K)/AKT signaling pathway, which is critical in controlling cell growth and proliferation during development and has been implied in multiple syndromes with tissue overgrowth. Activation of mTOR signaling increases the expression of VEGF, therefore contributing to increased angiogenesis and lymphangiogenesis[3].

Lymphangiomas management can be challenging due to their permeative growth throughout tissue layers. To date, there is no uniform guideline for the treatment of CL, which currently intends to control related symptoms, maintain functionality, and preserve aesthetic integrity[4].

Sirolimus, also known as rapamycin, is a serine/threonine kinase that regulates the signaling pathway PI3K/AKT/mTOR. It is typically well tolerated[3,4], with the most significant adverse effects being nausea, cytopenia (thrombocytopenia and anemia), and metabolic imbalances (hyperglycemia, hypercholesterolemia, elevated alkaline phosphatase, elevated serum creatinine, and hypophosphatemia)[2], especially in the beginning of the treatment.

There have been reports of the successful use of sirolimus in children with vascular malformations[1-4]. The possibility of oral administration with a comfortable scheme (two administrations daily) makes it easy for parents to administer and stimulates compliance to treatment.

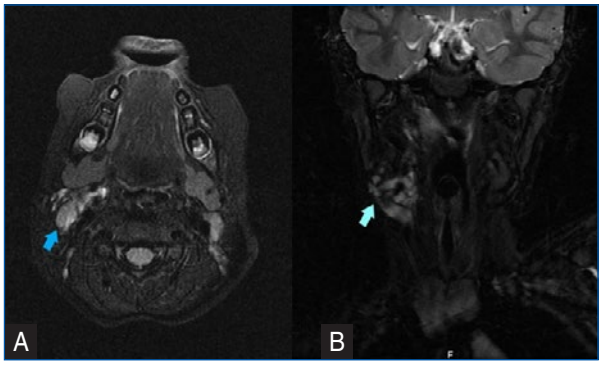

Figure 4. **A and B:** MRI images of the lymphangioma that was significantly reduced after treatment with sirolimus (blue arrow).

The optimal timing of treatment is yet to be determined, as there are no sufficient studies to state when to stop oral sirolimus in CLs.

In the case we described, there was good compliance to therapy and tolerance with no significant side effects reported during follow-up, adding evidence of the effectiveness and safety of oral sirolimus in the treatment of CLs.

What does this study add?

The data on the use of sirolimus in the treatment of vascular malformations are still scarce. With this case report we aim to demonstrate the role of sirolimus in the treatment of a macrocystic lymphangioma in a pediatric patient, highlighting its effectiveness and safety.

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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CASE REPORT

Nevus or melanoma in a tattoo: a diagnostic pitfall

Nevo ou melanoma sobre tatuagem: dificuldades diagnósticas

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Abstract

The authors describe a 61-year-old male patient with two previous melanoma who developed a pigmented lesion on a tattoo that was difficult to diagnose on dermoscopy but histopathology revealed the third melanoma with 0.3 mm thickness. The authors call the attention to increasing incidence of melanoma in the German population in parallel with the increase in tattooing, which may delay the diagnosis of melanoma in tattooed skin. Therefore, they recommend performing early biopsies in pigmented lesions in tattoos, especially before laser treatment of tattoos.

Keywords: Melanoma. Melanocytic nevi. Tattoo.

Resumo

Os autores descrevem um doente do sexo masculino com 2 melanomas anteriores com lesão pigmentada sobre tatuagem, cujo diagnóstico dermatoscópico não foi claro, mas cuja histopatologia confirmou tratar-se de melanoma com uma espessura de 0.3 mm. Os autores chamam a atenção para o crescimento tanto da incidência do melanoma como do número de indivíduos com tatuagens, o que poder atrasar o diagnóstico de melanomas que ocorram na pela tatuada. Recomendam assim a realização de biópsias precoces em lesões pigmentadas sobre tatuagens, especialmente antes do seu tratamento com Laser.

Palavras-chave: Melanoma. Nevo melanocitico. Tatuagem.

Case report

A 61-year-old man skin type II presented to our outpatient clinic with a suspicious lesion within a tattoo on his right upper arm for an unknown period of time. On examination, he had a soft, sharply demarcated bluish papule measuring 7 mm with a smooth surface. The papule could be pressed into the level of the skin. Incident light microscopy revealed blue lacunae outside the tattoo and blackish structureless portions in the area of the overlying tattoo (Fig. 1, black arrow). In addition, distal to the lesion described above, he had a symmetrical, irregularly pigmented, and approximately 5 mm in diameter brown macule. Incident light microscopy revealed an irregular internal structure consisting of reticular lines and clods with questionable heterochromia. The assessability to this lesion was considerably limited by the tattooing (Fig. 1, red arrow).

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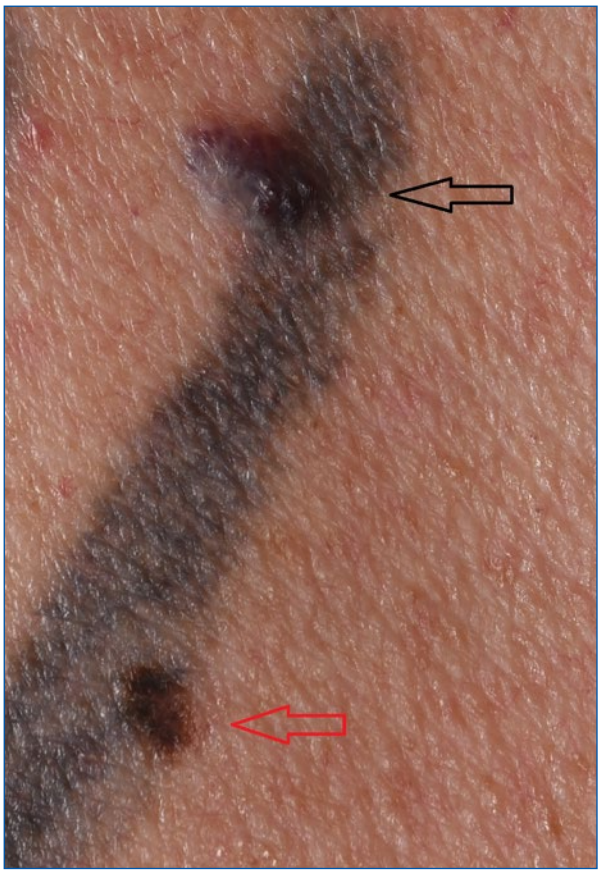

Figure 1. Two pigmented lesions over a black tattoo whose histopathology revealed an hemangioma (black arrow) and a melanoma explanation only in text (not beneath photo).

The patient's past medical history included diabetes mellitus, arterial hypertension, attention deficit hyperactivity disorder, benign prostatic hyperplasia, and fibromyalgia. He also reported a history of melanoma that had been excised from the back about 30 years earlier. The tumor data could no longer be obtained. Furthermore, a superficial spreading melanoma on the right thigh (tumor thickness 0.5 mm, Clark level II, < 1 mitosis/ mm^2, no nevus association) had been excised in our clinic 2 years prior. Both melanomas had occurred in non-tattooed skin. Follow-ups with a dermatologist had always been unremarkable. As a child, the patient suffered several sunburns.

The two lesions described above were excised under local anesthesia. Histology of the proximal lesion revealed a hemangioma (Fig.1, black arrow), and of the distal lesion (Fig.1, red arrow) a superficial spreading melanoma in the tattoo (Fig. 2 and 3), Clark level II, vertical tumor thickness- Breslow 0.3 mm (pT1a). There was no ulceration or regression.

Discussion

In the present case, tattooing occurred in the history of two malignant melanomas. A third melanoma developed in the black tattoo, which significantly complicated the diagnosis of the third melanoma during tumor follow-up, although we were still able to diagnose and remove the melanoma while it was in stage I. With already two pre-existing melanomas, skin metastasis can also be considered. These often appear to be dark, red, or skin-colored papules or nodules.

We interpret the hemangioma as incidental.

Early detection of malignant melanoma with the aim of excision at low tumor stages is a major goal of dermatologic screening. The rising incidence of melanoma in Germany is currently reported to be 26.5 cases (men) and 25.3 cases (women) per 100,000 inhabitants per year. For tattoos, a prevalence of 14% in Western countries and up to 50% among 25-35-year-olds are reported[1-5]. With the increasing incidence of melanoma coupled with the increasing prevalence of tattoos, a cumulative occurrence of melanoma in tattooed individuals must be expected.

To our knowledge, 36 cases of melanoma in tattoos have been reported in the literature to date. The risk for melanoma development does not appear to be increased per se in tattooed skin[6,7]. But morphologic evaluation is complicated by the exogenous pigment, resulting in a possible delay in diagnosis[8]. Suspicious nevi can be covered by tattoos so evaluating the nevi is extremely difficult at the clinical and dermoscopic levels. In addition to the generally more difficult assessability, especially dermal signs of malignancy, such as blue or gray veils, can be disguised by a tattoo. Therefore, tattooing must be viewed extremely critically in the presence of multiple and/or atypical nevi syndrome and melanoma in the patient's own and/or family history.

In addition, a thorough dermatologic examination should be performed prior to any laser therapy of a tattoo to avoid triggering changes in nevi or melanoma-specific lesions[9,10,11]. If laser therapy is specifically desired and indicated, we recommend excising pigmented lesions in the tattoo prior to laser therapy and submitting them to histologic examination. Regarding carcinogenic ingredients of tattooing products, a negative list exists in Germany since 2009, though it has not been established if avoiding these ingredients decreases malignancy risk[12]. In addition to the usual provisos, UV protection in the area of tattoos is recommended since UV radiation can potentially alter tattoo ingredients and lighten the tattoo under UV irradiation[13-15].

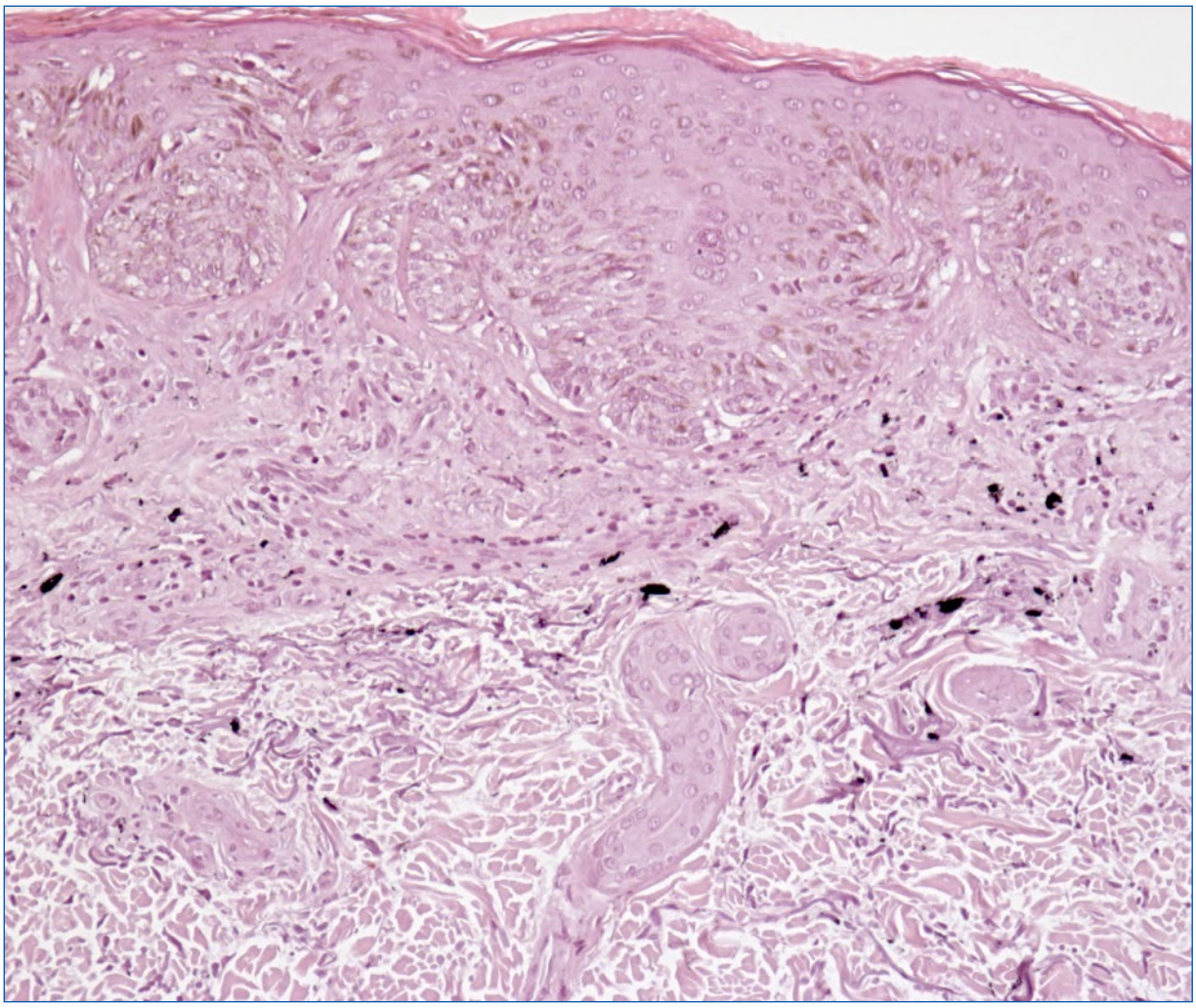

Figure 2. Irregular melanocytic proliferation with formation of nests of atypical melanocytes in the area of the junctional zone and in the adjacent corium. Proliferation of single atypical melanocytes in the basal cell layer with suprabasal storage, discharge into the stratum corneum. Inhomogeneous pigment incontinence and moderate inflammatory infiltrates. In addition, granular to scaly pigment deposits are found in the upper to middle corium. Also, solar elastosis. Diagnosis: superficial spreading melanoma in tattoo, Clark level II, vertical tumor thickness according to Breslow 0.3 mm, (pT1a). No ulceration. No regression. No nevus association.

Summary and conclusion

There should be a low threshold for performing biopsies in suspicious melanocytic lesions within a tattoo, as morphologic malignancy criteria may be obscured by the exogenous pigment.

Tattoos should be very carefully considered in people with multiple nevi syndrome, atypical nevi, and a history of melanoma in self and/or family. No tattoo should be applied in the area of nevi. People with this history should see a dermatologist prior to obtaining a tattoo and obtain regular skin checks after.

Although no correlation between melanoma development and tattooing has been found from the literature available to date, extreme caution should be exercised with tattooing in patients at increased risk for melanoma and prior to laser therapy.

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

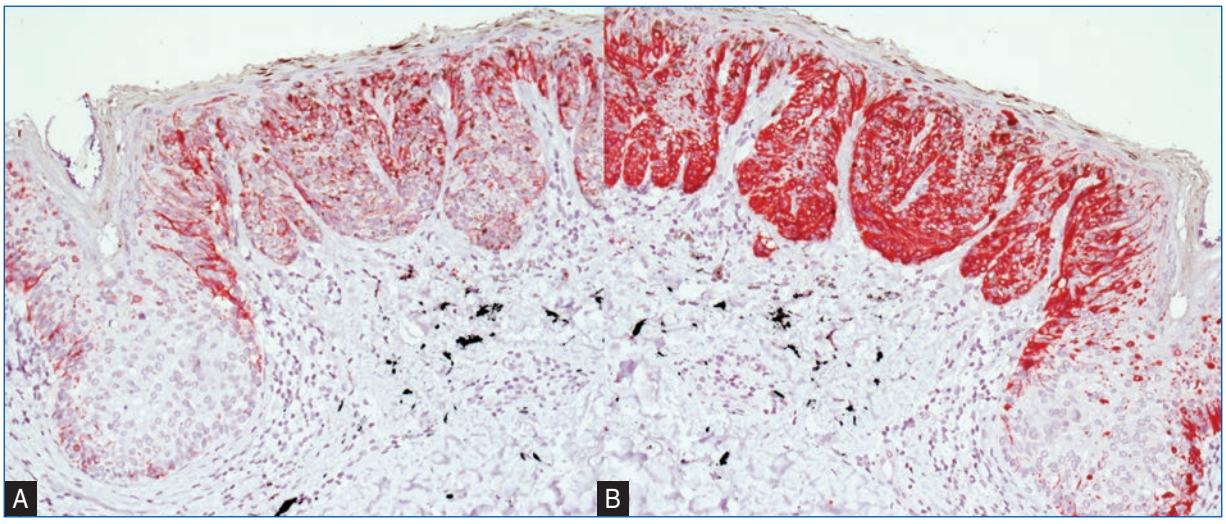

Figure 3. Immunostaining Melan A and HMB45. **A**: immunostaining with monoclonal anti-MART-1/MelanA-antibody (200x) MelanA-Staining marks melanocytes in all layers of the epidermis. **B**: immunostaining with monoclonal anti-HumanMelanomaBlack (HMB45)—antibody (200x) HMB45-Stainings marks premelanosome protein (PMEL) in proliferating melanocytes in all layers of the epidermis.

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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CASE REPORT

Insights into the development of lentigo maligna and dysplastic nevi: spotlight on the possible relation with sartans, thiazides and nitrosamines

Um olhar sobre fatores de risco de lentigo maligno e nevos displásicos: ênfase na possível relação com sartans, tiazidas e nitrosaminas

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Abstract

Since the alarming, yet prudent publication of the possible association of sartan use and development of various cancers in 2010, anti-hypertensive drugs (sartans and thiazide diuretics) have been closely monitored by various scientific and drug authoritarian bodies around the world. Fast forward 12 years, the number of scientific publications showing an increased risk of developing various types of cancer, including skin cancers, after sartan and/ or hydrochlorothiazide use is on the rise. **Case description:** A 77-year-old male with arterial hypertension under treatment for approximately 3 years (2018-2022) with three different preparations containing sartans in combination with hydrochlorothiazide was observed with a pigmented lesion present on the left cheek for 2 years with clinical and dermatoscopic suspicion of lentigo maligna, confirmed by histopathology. Further three suspected dysplastic *naevi* were also identified on the back, two of them confirmed by histopathology. Possible drug-induced melanocytic lesions were suspected and his drug regimen was changed. The prognosis was favorable with a good post-operative outcome. **Conclusion:** The amount of data linking the use of hydrochlorothiazide alone or in combination with sartans and the development of melanomas or their precursors, is worrying. Given the additional disclosure of pharmaceutical companies about the existing elevated concentrations of nitrosamines in these two classes of antihypertensive drugs, the establishment of a causal relationship between the intake of a particular carcinogen and the development of a tumor or tumor precursor requires careful and detailed scrutiny. The extent to which sartan/hydrochlorothiazide used and the occurrence of the lentigo maligna, especially when shared data points in this direction, remains unclear. However, in clinical practice, it should be highly recognized.

Keywords: Melanoma. Lentigo maligna. Antihypertensive therapy. Sartans. Skin cancer. Hydrochlorothiazide.

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Resumo

Desde a publicação referente à possível associação entre o uso de sartans e o aparecimento de vários tipos de neoplasias em 2010, de forma prudente o uso de fármacos antihipertensores (sartans e diuréticos tiazidicos) tem estado sobre monitorização por várias entidades científicas e reguladoras do marcado a nível mundial. Nos 12 anos seguintes tem aumentado o número de publicações relacionados com o risco de desenvolver diferentes tipos de cancro, incluindo cancros cutâneos, com o uso de sartans e/ou hidroclorotiazida. **Caso clínico:** Um homem de 77 anos com hipertensão arterial tratado por cerca de 3 anos (2018-2022) com 3 diferentes fármacos contendo sartans e hidroclorotiazida foi observado com lesão pigmentada da hemiface esquerda com 2 anos de evolução e aspetos clínicos e dermatoscópicos de lentigo maligno, confirmado por histopatologia, e 3 lesões sugestivas de nevos displásicos no dorso também confirmados por histopatologia. Dada a possível relação das lesões melanocíticas com os fármacos estes foram suspensos e o resultado cirúrgico e o prognóstico foram favoráveis. **Conclusões:** São alarmantes os dados associando o aparecimento de melanomas ou seus percursores ao uso de hidroclorotiazida, de forma isolada ou em combinação com sartans. A informação adicional das companhias farmacêuticas da presença de nitrosaminas nestas duas classes de fármacos antihipertensores, permite equacionar alguma possível relação entre o ingestão deste potencial carcinogénico e o desensolvimento de neoplasias, o que requer escrutineo exaustivo. A verdadeira extensão da relação sartan/hidroclorotiazide e lentigo maligna é ainda desconhecida mas quando dados apontam nesse sentido, não a devemos desprezar na prática clínica.

Palavras-chave: Melanoma. Lentigo maligno. Terapêutica antihipertensiva. Sartans. Cancro cutâneo. Hidroclorotiazida.

Introduction

Problems with the development of cancer after the use of sartans (*angiotensin receptor blockers*) date back to 2010 when their first use in patients with hypertension was associated with a negligible increased risk of developing various (or any type) of cancer[1]. Twelve years later, the same authors performed a meta-analysis with statistically "much more mature" considerations and concluded that the use of sartans for a longer period (over 2.5/3 years), as well as at the maximum daily dose, is clearly associated with a significant risk of developing cancer[2]. However, the dilemma regarding the mentioned issues- "Sartans, Nitrosamines, and Cancer"—became even more relevant and significant only in 2018, when the Food and Drug Administration (FDA) officially announced contamination of drugs for blood pressure, namely sartans, with nitrosamines, defined for decades as one of the most potent mutagens / carcinogens[3].

We present a patient who received three different types of sartans in combination with hydrochlorothiazide for about 3 years, who subsequently developed lentigo maligna in the left cheek, as well as two dysplastic *naevi*. The potential role of systemic medication (sartans and thiazide diuretics) and eventual contaminants in these drugs (nitrosamines) and important pathogenetic inducers for the development of melanoma and pre-melanoma melanocytic skin lesions is discussed.

Case description

A 77-year-old Caucasian male, phototype II, visited our policlinic for Dermatology, Venereology and Dermatologic Surgery in February 2022 with a primary complaint of a pigmented lesion on the left cheek (Fig. 1A), first noticed in January 2020 and which increased in size and discoloration over the last 2 years. Arterial hypertension diagnosed 11 years prior has been under treatment with olmesartan/hydrochlorothiazide 20/12.5 mg id for 2 months in 2018, followed by irbesartan/hydrochlorothiazide 150/12.5 mg id for 3 months in 2019 and since then telmisartan/hydrochlorothiazide 80/12.5 mg for about 2.5 years. No other drug history was reported.

Past medical history also revealed a prior malignant melanoma on the left arm surgically removed with an overall margin of 2 cm without performing an sentinel lymph node (SLN) biopsy with a thickness >2.5 mm with infiltration into the reticular dermis (Clark IV), without invasion of the lymphatic and venous vessels (T3aN0M0) and no evidence of disease progression on imaging studies on 2015, 2017, and 2019. Other compound nevi without dysplasia were removed on the left pectoral region back in 2015 and 2018. The patient reported no allergies or prior history of significant sun exposure, no family history of skin and other malignancies, including melanoma and social and living conditions were unremarkable.

Dermatological examination in 2022 showed a superficially spreading solitary macule measuring roughly 0.9 cm in diameter on the patient's left cheek

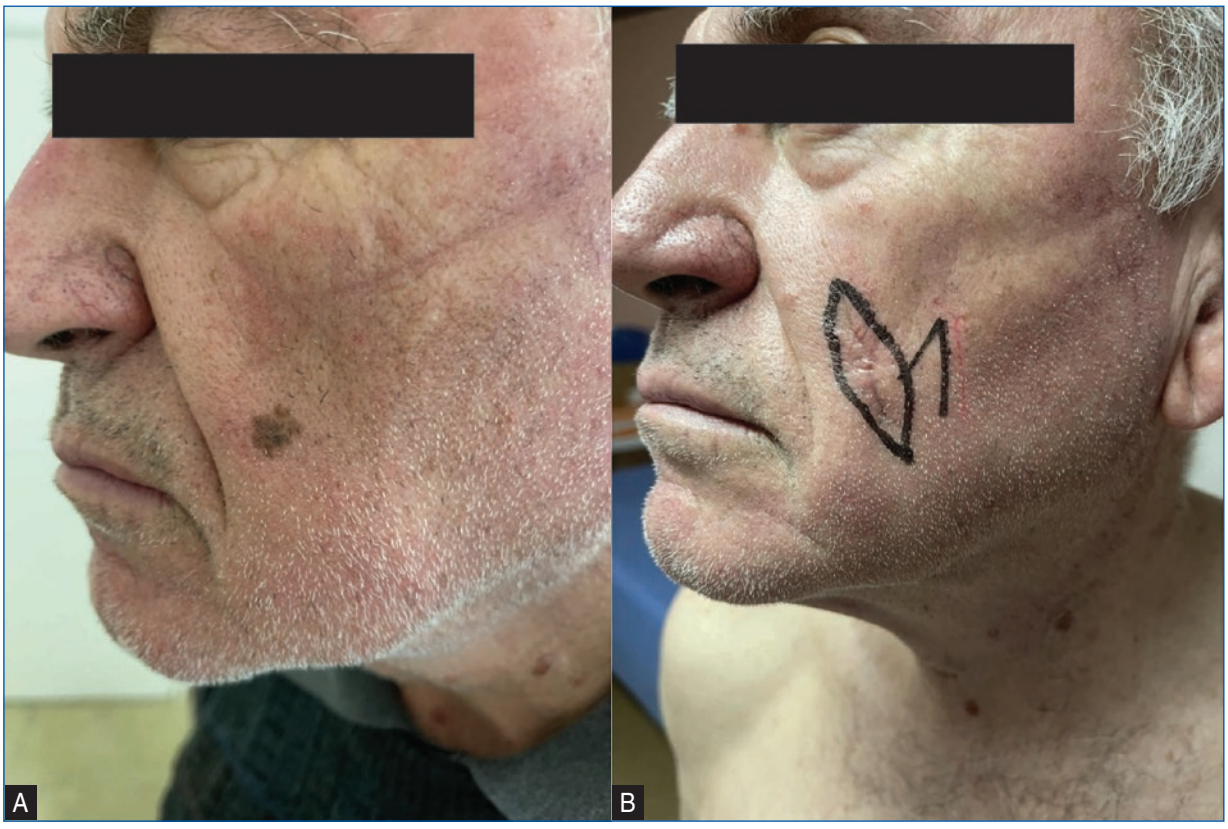

Figure 1. **A:** single superficially spreading, asymmetrical, hyperpigmented lesion on the left buccal region. Uneven borders, clear demarcation with varying shades of discoloration observed, confirmed as a melanoma on histopathology. **B:** clinical image of re-excision with preoperative surgical safety markings of an additional 1 cm in all directions.

region, next to the nasolabial fold (Fig. 1A) and three additional, irregularly shaped melanocytic *naevi* on the back (Fig. 2). The facial lesion was asymmetrical, unevenly bordered and with clear demarcated zones of varying shades of discoloration, mostly pronounced in its infero-lateral area, which according to the clinical and dermatoscopic evidence, was diagnosed as lentigo maligna. The other lesions localized on the scapular region, infra-scapular, and lumbar regions had positive ABCD criteria (asymmetry, irregular borders, discoloration, and diameter > 6 mm) (Fig. 2), and were diagnosed as melanocytic *naevi* with dysplasia.

With the suspicion that telmisartan/hydrochlorothiazide might contribute to the melanocytic lesions this medication was discontinued and an alternative treatment regimen of torsemide 10 mg/day, moxonidine 0.4 mg/day and flecainide acetate 100 mg 2id was prescribed with good blood pressure control.

The facial lesion was removed, under local anesthesia, in the form of an elliptical excision with a resection field of 0.1-0.3 cm and as histopathology confirmed a melanoma *in situ*, lentigo maligna type, a secondary excision for an additional surgical safety margin of 1 cm in all directions was performed (Fig. 1B) with clean resection margins. Histopathology of the three melanocytic *naevi* in the back confirmed dysplastic melanocytic naevi in two of them, with clean resection margins. Post-operative outcome was positive with good signs of wound healing for all four lesions. A 4-week follow-up visit showed no signs of complication or other concerns.

Discussion

As a subtype of melanoma in situ, lentigo maligna clinically presents in areas of sun-exposed skin and is more common in the elderly population[4]. This is due to chronic UV radiation as a key risk factor that has been shown to propagate BRAF, KIT, and TP53 mutations in melanoma[4,5]. Patients who develop melanoma are also at a higher risk of developing further or recurrent melanocytic lesions[5]. While many factors may influence the initiation and/or potentiation of such cancers, the exact etiological agent cannot be properly established[5]. As a result, identification of every possible risk factor is

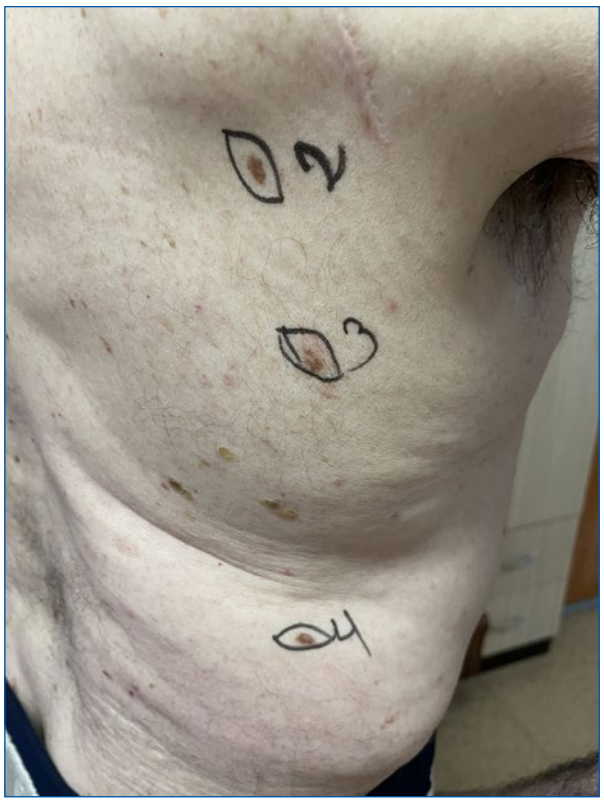

Figure 2. Additionally, three melanocytic naevi on the back.

essential for achieving further cancer prevention. Antihypertensive drugs, such as sartans and thiazide diuretics, as well as non-antihypertensives such as ranitidine and metformin, have been found to be associated with an increased risk of developing both cutaneous as well as non-cutaneous cancers[6,7,20,21]. The exact mechanism is largely unknown but there is increasing evidence suggesting the contamination of these drugs with nitrosamine is the main culprit[6,7].

One of the latest or most recent scientific publications from 2021 emphasizes the importance of nitrosamine-contaminated valsartan and the risk of cancer[8]. Statistical analysis indicates a 3-fold to 4-fold increased risk of developing cancer (per 100,000 people) in the presence of N-Nitrosodimethylamine (NDMA) or N-Nitrosodiethylamine (NDEA) contamination[8]. The first experimental data from 2018 linked sartans, and in particular losartan, with the possibility of potentiating metastasis of pre-existing melanoma cells in the laboratory[9]. The ability of sartans (again losartan) to potentiate melanogenesis/carcinogenesis was confirmed in a subsequent multi-center experimental study a year later[10]. The limitation of both laboratory tests is mainly the lack of data on whether the active substance used (losartan) contains or is contaminated with nitrosamines such as NDMA, NDEA for example.

Clinical data from retrospective observations available in the literature, are even more interesting and completely support this relation[11,12]. A retrospective analysis conducted in 2015 in patients taking sartans found that a long-term low dose of sartans was associated with a 53% risk of developing melanoma (OR: 1.53: 95% CI [1.05-2.23]), while long-term high-dose sartans have been associated with a 44% risk of developing melanoma (OR: 1.44: 95% CI [0.56-3.69])[11]. In 2017, an even more comprehensive retrospective analysis of an American team tracking the development of various forms of skin cancer after antihypertensive drugs concluded that:

1. Monotherapy with angiotensin receptor blocker could be associated with the development of melanoma, with a risk ranging between 24 and 225% depending on its stratification: unadjusted odds ratio (95% confidence interval): 2.25 (1.73-2.94)/adjusted OR (95% CI): 1.24 (0.54-2.85)[12], and
2. Monotherapy with thiazide diuretic is associated with a relatively constant risk of developing melanoma (with and without risk stratification): unadjusted OR (95% CI): 2.06 (1.59-2.66)/adjusted OR (95% CI): 1.82 (1.01-3.82)[12].

In both clinical studies, there were no data on whether patients were taking preparations contaminated with nitrosamines or "purely" free from this component[11,12]. Nevertheless, analyzing the shared data[12], it could be concluded that in certain cases (combined use of sartans and hydrochlorothiazide) the risk of developing melanoma could be increased up to 4-fold.

Also, in the world literature described, there are several clinical reports of melanoma developing after monotherapy with sartans or sartans in combination with hydrochlorothiazide[13-17]. The single casuistry is also supported by large-scale, albeit still retrospective, follow-up of patients taking hydrochlorothiazide and developing melanoma, similar to the lentigo-maligna type, as in our case[18]. They found a 57% risk of developing lentigo maligna after taking hydrochlorothiazide[18].

The potential contamination of diverse types of medications with nitrosamines has been associated since 2021 with a possible risk of developing melanoma in the bulletins of DRUG WATCH/FDA[19,20]. Therefore, in practice, it is quite possible that the nitrosamine NDMA, found in medications such as

ranitidine or sartans (according to the FDA Bulletin 2021), can contribute to the potentiation/induction of melanoma[19,20]. Interestingly, however, and although there is no evidence in the literature (or no single publication) on the development of melanoma after taking NDMA-contaminated ranitidine, melanoma is listed in the 2021 FDA/Drug Watch bulletin as a potential candidate for compensatory claims related to the same drug- ranitidine[19,20]. However, for unknown reasons, NDMA does not appear in the FDA/DRUG WATCH compensation claims bulletin for medicines containing sartans or sartans/hydrochlorothiazide contaminated or potentially contaminated with NDMA. It is more conspicuous now, after Pfizer, one of the biggest pharmaceutical companies worldwide has conducted voluntary nationwide recalls of the drug quinapril hydrochlorothiazide due to the presence of nitrosamine above the acceptable daily intake (ADI) level[21]. With this data, alongside the vast recalls from the FDA, it is clearly evident that nitrosamine contamination within sartans, thiazide diuretics and other drugs like ranitidine and metformin is a major issue[19,21].

It cannot be refuted that nitrosamines, as carcinogens, can initiate and even potentiate tumorigenesis in melanoma[22]. Studies have also shown that patients actively taking valsartan with a combination of hydrochlorothiazide have developed cancers including colon carcinoma, Kaposi sarcoma besides cutaneous melanoma[23,24]. While certain meta-analyses suggest "no-associated risk" between anti-hypertensives and skin cancer[25,26], it is not clear whether the drug batches were contaminated with nitrosamines or not, which may also depend on the geographical regions and stricter controls of contamination during the manufacturing process. The vast diversity in such meta-analytical data, especially when there are other scientific publications, including meta-analyses, opposing these findings[1,2,6-18], suggests perhaps an underlying issue is being missed. The step up in international inspections and the subsequent findings of elevated nitrosamine contamination, as well as the vast recalls of drug batches (by FDA, and now Pfizer) in antihypertensives and other commonly prescribed drugs such as ranitidine and metformin due to nitrosamine contamination merits further assessment by the scientific community[19-21].

Although our patient did not report any prior history of sunburn, it is difficult to rule out the role UV exposure. But, it is important not to rule out other possible risk factors, especially the possible nitrosamine contaminated batches of olmesartan, irbesartan, and telmisartan in combination with hydrochlorothiazide (also a potential nitrosamine contaminated drug) that he took for 3 years.

With the recent introduction of permissible concentrations of nitrosamines in antihypertensive drugs, the additional risk of a cumulative effect also cannot be ruled out, especially as there have been three different drugs (in combination with hydrochlorothiazide) used by the patient[27]. Interestingly, foods, water, and tobacco that are known to have small amounts of nitrosamine have been unaccounted for and could tip the balance over the ADI level, even if trace amounts were found in each individual drug for example[28]. The lack of follow-up evidence especially with the calculation of such data can be problematic to discern the real culprit behind the pathological process of such cancers. Although these associations are difficult to ascertain from isolated case reports, it is important not to disregard the increasingly troubling data that ultimately affects the patient on an individual level and strengthen the relation between sartans, nitrosamines, and melanoma[11-17].

In the present case, the patient developed a melanocytic lesion prior to starting his medication in 2019, therefore the pathological mechanisms are most likely multifactorial in nature, especially with his advanced age and possible long-term UV exposure. However, the possible role of sartans (in a combination of hydrochlorothiazide), particularly through nitrosamine contamination, should not be ignored, as nitrosamines are known not just to initiate tumorigenesis through induction of genetic mutagenesis but also to potentiate and facilitate neoplastic progression[27-29]. This potentiating effect could explain the short-term exposure in our patients. Additionally, photosensitization of the thiazide diuretic attributed to TP53 mutations and subsequent risk of melanoma may also play a role in the initiation of tumorigenesis alongside a cumulative effect UV radiation[29]. Such observations warrant a closer assessment of these drugs and addressing the nitrosamine contamination as well as the underlying synergism with other risk factors are the next steps in the right direction.

Conclusions

We present an interesting patient with arterial hypertension treated for approximately 3 years (2018-2022) with 3 different preparations containing olmesartan, irbesartan, and telmisartan, all in combination with hydrochlorothiazide, who developed lentigo maligna and dysplastic naevi. The potential role of sartans,

nitrosamines, and hydrochlorothiazide as possible triggers of carcinogenesis are discussed.

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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CASE REPORT

Complete hair regrowth in a young male with severe atopic dermatitis and alopecia areata after dupilumab: probably more than a coincidence

Repovoamento completo num adulto jovem com dermatite atópica grave e alopecia areata após dupilumab: provavelmente mais do que coincidência

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Abstract

We report the case of a 29-year-old male patient who has suffered from severe atopic dermatitis (AD) since early childhood and presented with a 6-month evolution of patchy hair loss in the temporal and occipital regions, clinically suggestive of alopecia areata (AA), which was confirmed by scalp biopsy. The patient started therapy for atopic dermatitis with the monoclonal antibody dupilumab, with a substantial response regarding atopic dermatitis, and with renewed hair growth on the scalp. Dupilumab blocks the α-subunit of the interleukin 4 receptor, interrupting the signaling cascade of IL-4 and IL-13 and thus leading to a reduced Th2 immune response. Some controversy exists regarding dupilumab and AA, with some reports describing improvement after starting this drug while others showing patients with dupilumab-induced alopecia. The patient demonstrated dramatic improvement in both AD and AA early on and tolerated the drug without significant side effects. His quality of life was significantly improved. Patient selection could play a crucial role in the future, and the predictors of a good response are currently being identified so the responders with severe atopic dermatitis and alopecia areata could benefit from dupilumab.

Keywords: Alopecia areata. Dupilumab. Atopic dermatitis.

Resumo

Relatamos o caso de um doente do sexo masculino de 29 anos com dermatite atópica (DA) grave desde a infância com um quadro com 6 meses de evolução de perda de cabelo em padrão irregular nas regiões temporal e occipital clinicamente compatível com alopecia areata (AA), o que foi corroborado com biópsia do couro cabeludo. O doente iniciou terapêutica com o anticorpo monoclonal dupilumab, com melhoria substancial da dermatite atópica e com rápido repovoamento do couro cabeludo. O dupilumab bloqueia a subunidade α do receptor da interleucina 4, interrompendo a cascata de sinalização da IL-4 e IL-13 e reduz assim a resposta imune Th2. Existe alguma controvérsia em relação ao dupilumab e à AA, com alguns estudos a descrever melhoria após o início do fármaco, enquanto outros relatam doentes com alopecia induzida por dupilumab. O doente

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demonstrou melhoria dramática quer da DA, quer da AA precocemente e tolerou o fármaco sem efeitos colaterais significativos. A qualidade de vida melhorou significativamente. A seleção de doentes poderá desempenhar um papel crucial no futuro, com os preditores de uma boa resposta a serem identificados para selecionar os potenciais doentes com dermatite atópica grave e alopecia areata com a melhor resposta ao tratamento.

***Palavras-chave*:** Alopecia Areata. Dupilumab. Dermatite Atópica.

Introduction

Alopecia Areata (AA) is an autoimmune disorder characterized by nonscarring hair loss with preservation of the hair follicle, affecting up to 2% of the general population and imposing a significant psychological impact on affected patients[1].

AA can present in multiple patterns, and its severity may range from episodes of well-defined patchy hair loss on the scalp to the more serious and complete scalp (alopecia totalis) and total body hair loss (alopecia universalis)[2].

The theory of loss of the immune privilege of the hair follicle is thought to play a crucial role in AA[3]. The presumed target antigen is yet to be defined. The succeeding loss of hair follicle immune privilege results in the recognition of hair follicle autoantigens by autoreactive $CD8^+$ T cells[4]. Patients with AA have a constellation of potentially associated autoimmune conditions and an increased risk of Atopic Dermatitis (AD)[3].

Common treatment options for extensive AA, where intralesional and topical treatments are often of restricted applicability, include systemic immunosuppressants like methotrexate and cyclosporin, which generally provide temporary responses and are unsuitable for long time use[5]. Thus, there is a great demand for new, specific treatments for long-term disease control in moderate-to-severe AA.

Indeed, recent evidence suggests that Dupilumab, a monoclonal antibody directed against the IL-4 receptor α subunit blocking both IL-4 and IL-13 signaling and currently approved for the treatment of atopic dermatitis, could be of some benefit in AA[6].

Baricitinib, a Janus kinase inhibitor, has been approved for severe AA and other drugs from this class are presently undergoing clinical trials with positive preliminary results[7].

Cases have been reported of the improvement of AA in patients with concomitant AD receiving treatment with dupilumab[8].

The effect of dupilumab in AA has been postulated to be the inhibition of Th2 pathway activation found in AA scalp lesions[9]. Nevertheless, dupilumab has also been associated with AA both in patients with preexisting AA and those without a prior diagnosis of AA[10].

Case synopsis

A 29-year-old man was evaluated due to uncontrolled AD. He had a history of recurrent flares of AD since childhood with worsening in the last 2 years. He also had a 6-month history of round patchy hair loss.

He had AD from the age of 3, with severe itching, sleep deprivation, and a great impact on his quality of life and was on an almost persistent use of topical corticosteroids and calcineurin inhibitors and occasional courses of systemic therapies with prednisolone as well as cyclosporin with limited and transient benefit. He reported asthma in childhood with spontaneous improvement and no current need for therapy.

Of relevance, he also had an episode of eczema herpeticum and herpetic keratoconjunctivitis treated with intravenous acyclovir a couple of weeks prior to the observation.

On physical examination, multiple erythematous papules and plaques, some of which were severely excoriated by scratching, were found on the entire skin including the face, cervical region, flexures of the forearm, and knees. EASI score was 14,6. He also had several patches of alopecia on occipital, temporal, and parietal regions, with scaling and erythema (Fig. 1). The eyebrows, eyelashes, and body hair was spared.

Laboratory tests were normal (hemogram with differential blood count, kidney, liver and thyroid function, and electrolytes) except for increased serum IgE levels (3055.3 IU/mL). Trichoscopy showed yellow and black dots and a perifollicular scale. Two 4 mm punch biopsies were performed on the scalp, showing dermis with adnexal rarefaction, presence of a sebaceous component, and fibrosis with a mild lymphocytic infiltrate and "stela" like structures, favoring the diagnosis of alopecia areata.

He was started on dupilumab with an initial dose of 600 mg followed by 300 mg every 2 weeks.

The patient was observed to evaluate the response 16 weeks after the first dose of dupilumab, with a

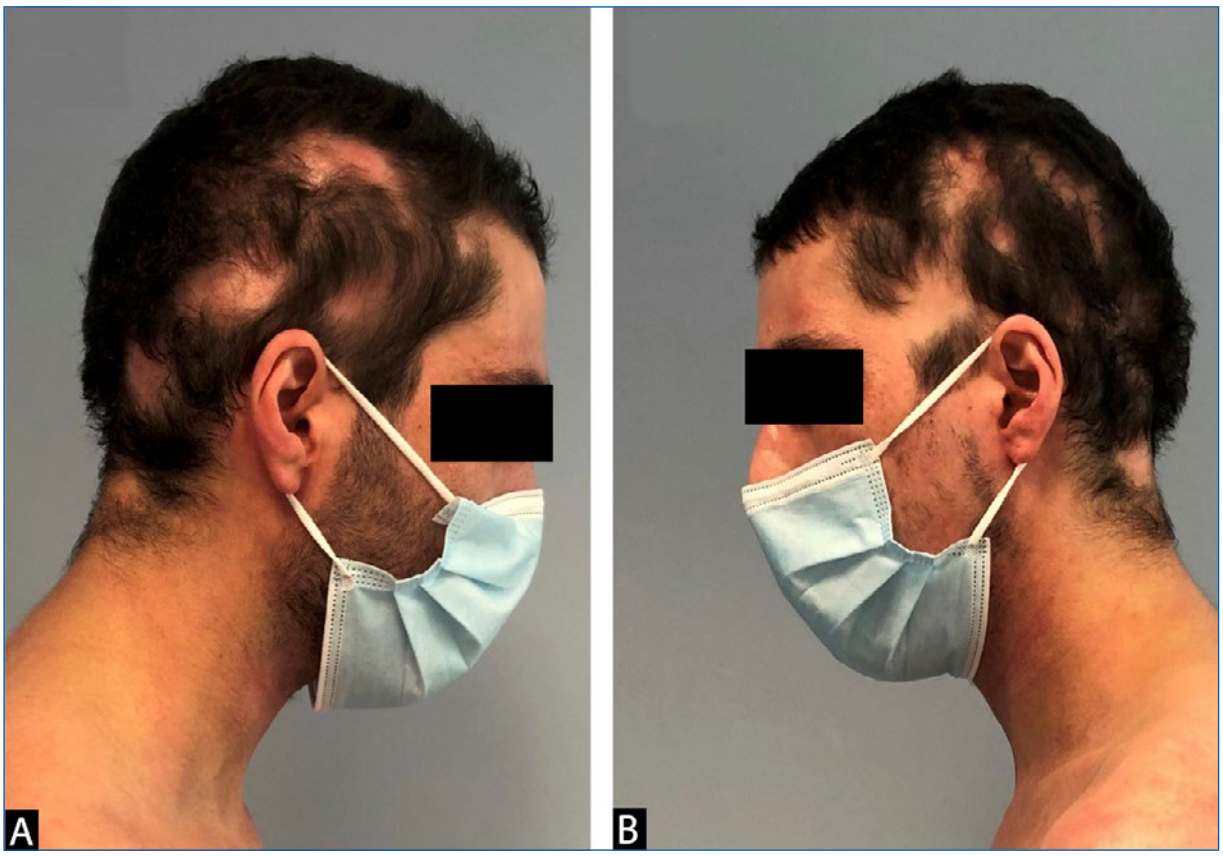

Figure 1. A and B: patches of alopecia on occipital, temporal, and parietal regions, with scaling and erythema.

dramatic improvement regarding atopic dermatitis with an EASI drop close to 0 and a resolution of the itching, a better sleep pattern and no need for any topical therapy except emollients. He also had full hair regrowth in the areas previously affected by AA (Fig. 2).

Except for slight conjunctivitis, which was successfully treated with artificial tears, the patient had no side effects and so far has tolerated the medication extremely well.

Discussion

Patients with AA show elevated levels of type 2 cytokines suggesting that Th2 axis suppression may be a therapeutic target for AA[9]. As dupilumab-induced IL-4 inhibition results in a decrease in inflammatory mediators, it likely leads to concomitant improvement of both AA and AD[11].

According to previous reports, hair regrowth with dupilumab usually begins between 3 and 6 months of therapy, although it may begin earlier[12].

However, the relationship between dupilumab and alopecia areata remains controversial as some patients experience improvement after starting treatment while others develop dupilumab-induced alopecia[13] with some studies suggesting that Th2 inhibition may amplify alternate pathways such as Th1 and Th17 resulting in hair loss[14]. Moreover, alopecia associated with dupilumab tends to follow an androgenetic pattern and usually has an eczematous pattern upon histopathological examination[15]. It is unclear whether dupilumab induces true AA or a form of drug-induced alopecia.

Janus Kinase Inhibitors have shown efficacy for moderate-to-severe AA[16]. In this case, baricitinib could have been an option due to the coexistence of AA and AD. However, due to the recent eczema herpeticum, we opted for dupilumab due to its safety and were extremely pleased by the effect on hair regrowth.

However, we should highlight that the temporal relationship between dupilumab use and AA hair regrowth does not ensure causality, as there may be

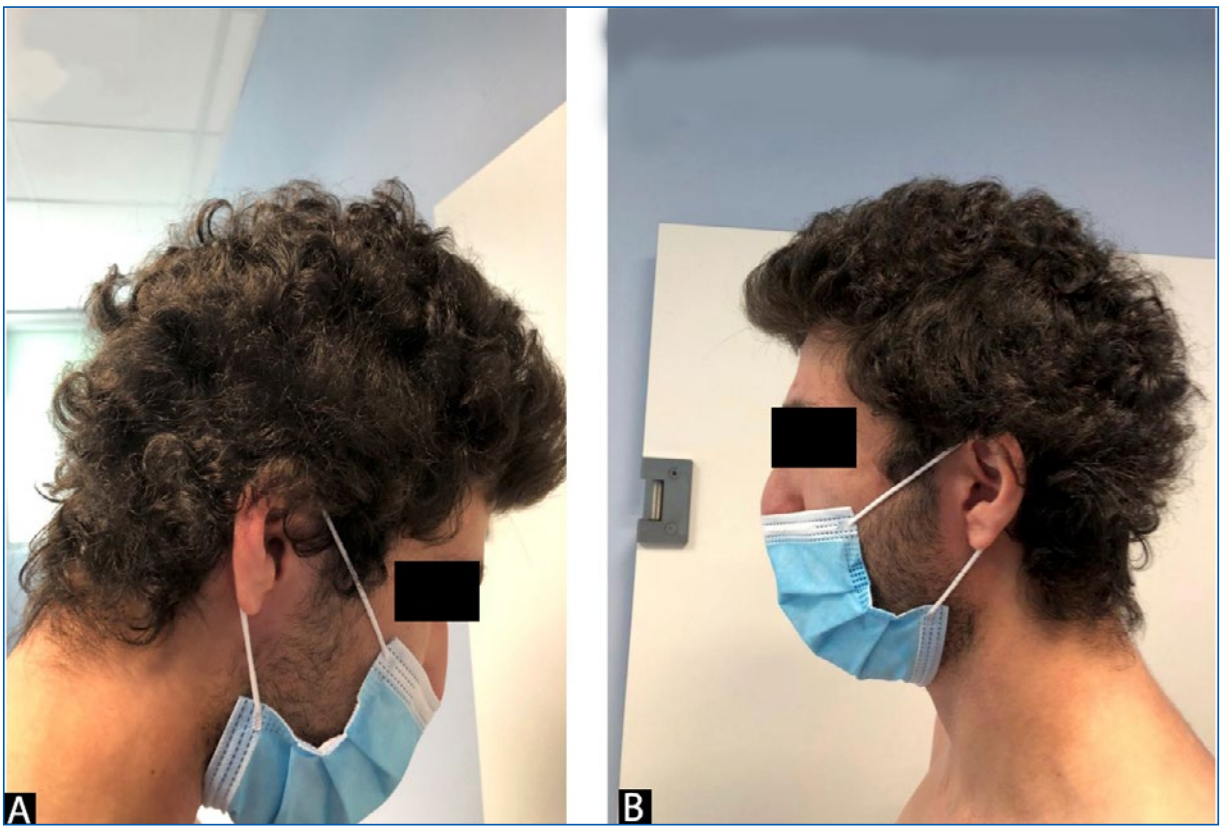

Figure 2. A and B: hair regrowth after 16 weeks of treatment with dupilumab.

spontaneous AA improvement. Therefore, we cannot attribute this fast improvement to dupilumab with certainty.

A study using the VigiBase, a real-world pharmacovigilance database concluded that hair disorders corresponded to 2.2% of total dupilumab adverse events. This study concluded that dupilumab was associated with both hair growth and loss and overall, the paradoxical results of dupilumab in hair disorders might be caused by complex disease factors, such as IgE and IL-4 levels and the complexity of AA pathogenesis[14].

A clinical trial has recently demonstrated the pathogenic role of the Th2 axis in AA and the efficacy of dupilumab in moderate-to-severe AA[17]. Furthermore, this trial showed that patients with IgE ≥ 200 IU/mL had an odds ratio of 8.1 to respond to dupilumab treatment compared to those with low baseline IgE, suggesting that IgE may be a tool for patient selection for dupilumab treatment, a new concept in AA management. A possible explanation for these findings may be that increased levels of serum IgE are indicative of Th2 -associated inflammation in the hair follicle, which may respond better to Th2-targeting approaches[17].

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None to declare.

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).

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IMAGES IN DERMATOLOGY

Elderly man with macroglossia and periorbital ecchymosis

Idoso com macroglossia e equimoses periorbitais

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A Caucasian 70-year-old male was observed with macroglossia with hemorrhagic spots and dental impressions on the border of the tongue, eyelid ecchymosis (Fig. 1), multiple brownish, lichenified papules and plaques, and diffuse ecchymosis on the neck and upper trunk (Fig. 2). Lesions were pruritic and progressively developed during 6 months. No systemic symptoms, except fatigue.

Skin biopsy of a papular lesion on the upper trunk showed epidermal atrophy and diffuse dermal deposition of proteinaceous amorphous material colored with Hematoxilin & Eosin (HE) and further enhanced with Congo red stains (Fig. 3). This material showed green birefringence peculiar on polarized microscopy.

Protein electrophoresis showed a peak of gamma fraction and immunofixation showed a monoclonal $IgG_{K,}$ with normal IgA and IgM. Bone marrow (BM) biopsy showed hypercellularity for age (in the three hematopoietic series) and the immunohistochemically panel showed BM infiltration by plasma cell neoplasia with evident lambda light chain restriction, confirming the diagnosis of multiple mieloma (MM). Neither osteolytic lesions nor the involvement of any other organ were detected.

The diagnosis of light chain (AL) amyloidosis associated with MM was done. The patient is being followed up together with onco-hematology staff, undergoing chemotherapy with Melphalan® and Prednisone, with satisfactory evolution (important improvement in pruritus and mucosal lesions, stability of skin lesions, and the patient's general condition).

Discussion

Amyloidosis comprises a heterogeneous group of diseases with extracellular amyloid deposits[1]. AL amyloidosis occurs in 5-26 % of patients with MM[1,2], and originates from the deposition in the skin and other organs of amyloid substance derived from monoclonal light chain immunoglobulins, leading to a plethora of clinical symptoms, and eventually vital organ dysfunction[3]. Lambda light chains are the most involved (3:1);[3-5] however, in the present case kappa light chain was preponderant.

The age range of involvement is between 50 and 70 years, with a slight male predominance[5]. The clinical manifestations are variable and nonspecific (weight loss, fatigue, paresthesia, and syncope) contrasting with highly suggestive dermatological manifestations: macroglossia with tongue hardening, with or without bleeding spots and blisters in the oral cavity; periorbital ecchymosis (raccoon sign) and ecchymosis due to minor trauma in the folds; translucent, purpuric and/or brownish papules on the scalp, face, neck, and fingertips; which may be the only manifestations of the

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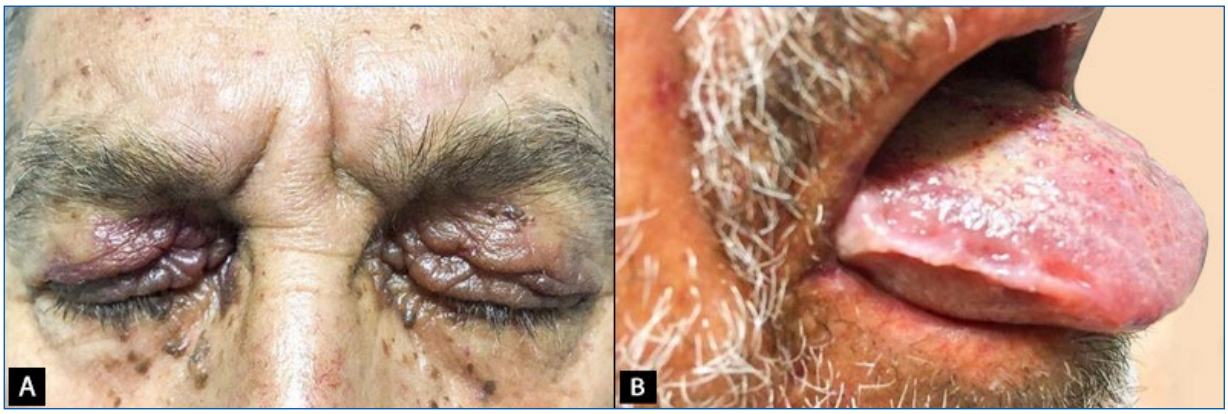

Figure 1. A: ecchymosis on eyelids. **B:** macroglossia with dental impressions and bleeding spots.

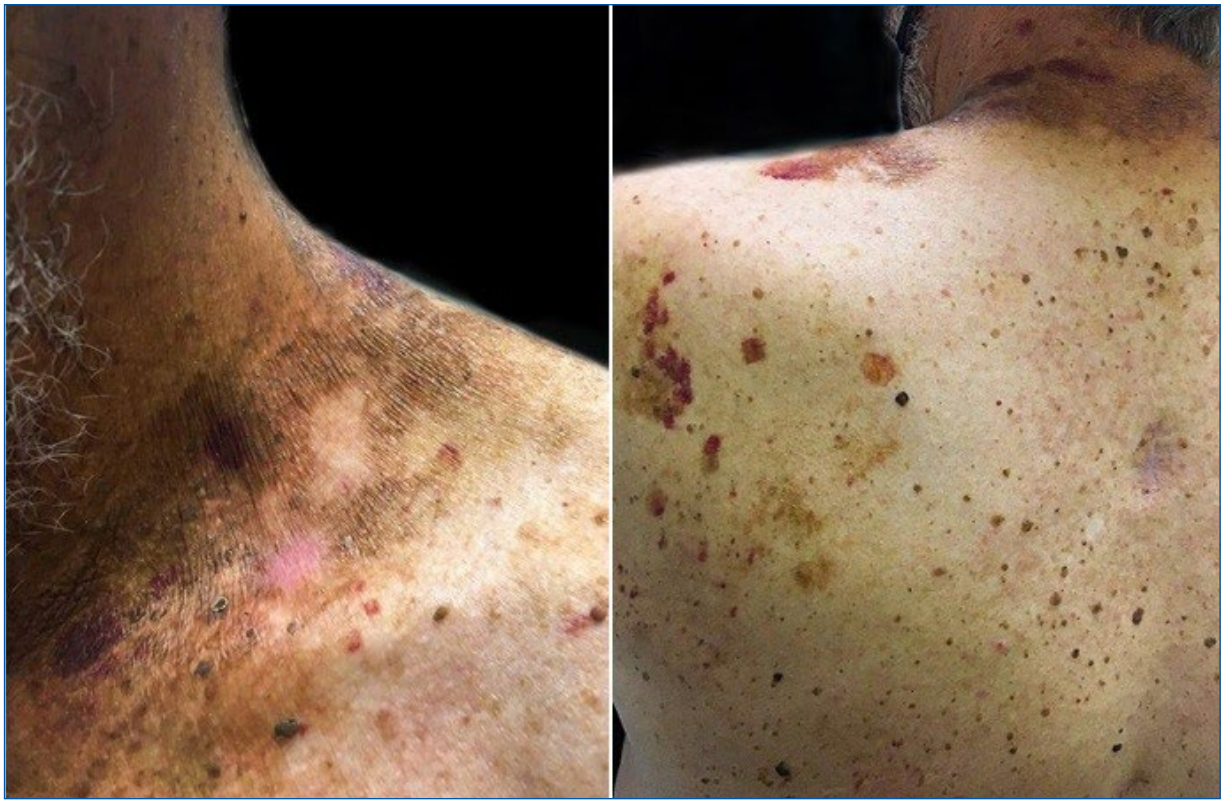

Figure 2. Diffuse ecchymoses and brownish lichenified papules and plaques, in cervical region and trunk.

disease prior to later-stage organ involvement, at which point treatment options are limited[1-6].

All forms of amyloid show a peculiar green birefringence on microscopy after staining with Congo red, the gold standard for diagnosis[5,6].

In the present case, the histopathological examination (HE and Congo red) and the monoclonal peak of the gamma fraction on protein immunoelectrophoresis confirmed the diagnosis of AL amyloidosis. Hypercellularity for age in the BM biopsy and the immunohistochemical panel showing BM infiltration by plasma cell neoplasm with evident lambda light chain restriction concluded AL amyloidosis was associated with MM.

As for the treatment, it aims to reduce the proliferation of the clonal B cell lineage and consequently the amyloid deposit, being the same used for MM (in the present case Melphalan® associated with Prednisone)[1,6]. Prognosis reserved[1,5,6].

The rarity of this case (association), the importance of early diagnosis (minimizing/delaying the amyloid

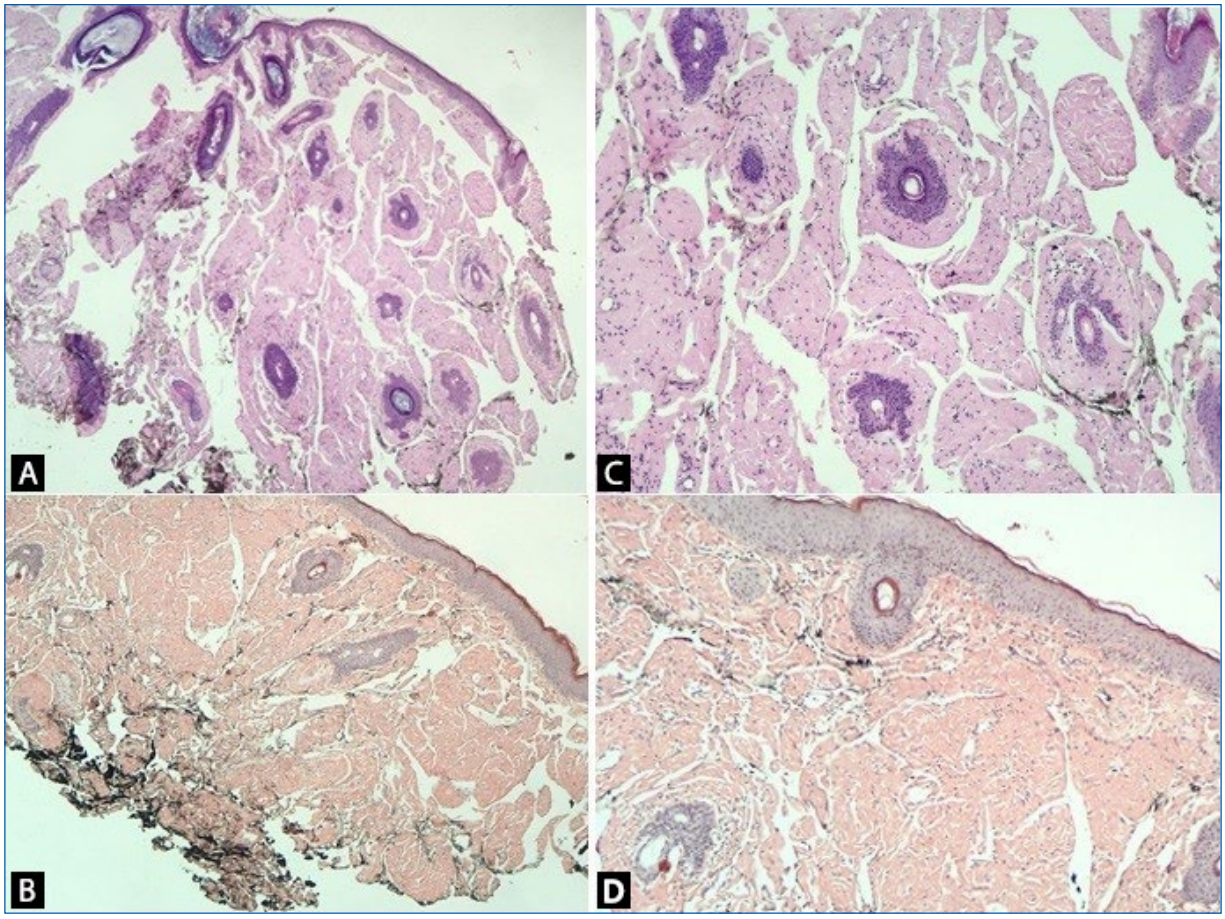

Figure 3. Histopathological examination. **A and B:** positive protein material in HE. **C and D:** Red Congo stains.

deposit) and the fundamental role of the dermatologist in this context, motivated this report.

Acknowledgments

To Dr. Fátima Maria de Oliveira Rabay and the onco-hematology staff for the clinical management of this case and to Dr. Fernanda da Rocha Gonçalves for the diagnostic assistance and histopathological images.

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Conflict of interests

None

Ethical disclosures

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IMAGES IN DERMATHOLOGY

Nail fold capillary abnormalities in dermatomyositis using a handheld dermatoscope

Anomalias capilares da prega ungueal na dermatomiosite usando um dermatoscópio manual

Tiago Fernandes Gomes[1,2,a], Rebeca Calado[1,b], Luísa Matos[1,c], and Margarida Gonçalo[1,3,d]

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Nailfold capillaroscopy (NC) is a non-invasive imaging technique used in the evaluation of the nailfold capillary network through the intact skin. Its role in the management of connective tissue disorders has been widely described, particularly in systemic sclerosis[1]. Previous studies have shown its value in the diagnosis and monitoring of dermatomyositis (DM)[2]. The active involvement of the vascular endothelium in DM induces a complement mediated microangiopathy, with clinical capillary abnormalities in the proximal nail fold (PNF)[2].

Although the videocapillaroscope is considered the gold-standard to evaluate nailfold microvascular damage[3], this equipment is not widely available in clinical practice, particularly in a dermatology office. Handheld dermatoscope (HD) can partially overcome the lack of videocapillaroscopes[3].

The authors report the use of a HD (Dermlite© DL4, × 10 magnification) in a quick and easy evaluation of the PNF capillaries in two patients with DM.

The first patient is a 67-year-old female with DM for 4 years, currently treated with mycophenolate mofetil 2 g/day and prednisone 10 mg/day. Her medical history included inverted and ulcerated Gottron papules, hypomyopathic myositis, and severe interstitial lung disease with pneumomediastinum and cutaneous emphysema, followed within 3 years by breast cancer. Serum myositis autoimmunity panel was positive for anti-SSA2 and anti-MDA5.

At her follow-up visit, skin manifestations of DM as well as lung disease were under control. NC of her digits using a HD revealed enlarged capillaries, microhemorrhages and hyperkeratotic yellow scale in the PNF of some digits (Fig. 1).

The second patient is a 35-year-old female diagnosed with a 3-year history of DM and breast cancer. No other systemic involvement was present. She was submitted to surgery, chemotherapy and radiotherapy for her cancer. Currently, she is medicated with hydroxychloroquine and topical steroids. Serum work-up detected anti-TIF1-γ autoantibodies.

At her follow-up appointment, she presented heliotrope rash, Gottron papules, and an itchy poikiloderma of her upper dorsum. Handheld dermoscopy of the PNF revealed enlarged and ramified capillaries and microhemorrhage (Fig. 2).

NC is a useful tool for diagnostic purposes in DM. Ramified and giant capillaries, microhemorrhages, vascular disorganization and capillary loss are some of the findings encountered in DM[1,2,4]. Improvement of the NC abnormalities is expected with the disease stabilization[4], although this was not the case in the first patient.

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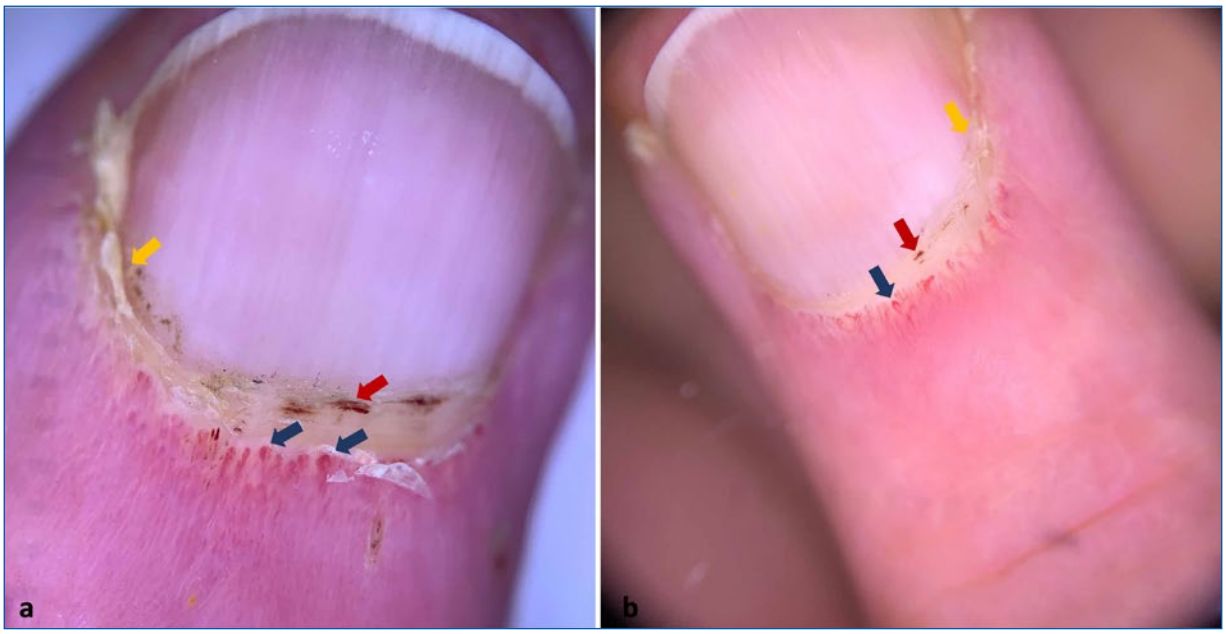

Figure 1. Nailfold capillaroscopy using a handheld dermatoscope in the evaluation of patient 1. Enlarged capillaries (blue arrows–a, b), microhemorrhages (red arrows–a, b) and periungual yellow scale (yellow arrows–a, b) are present. (Dermlite© DL4, x10).

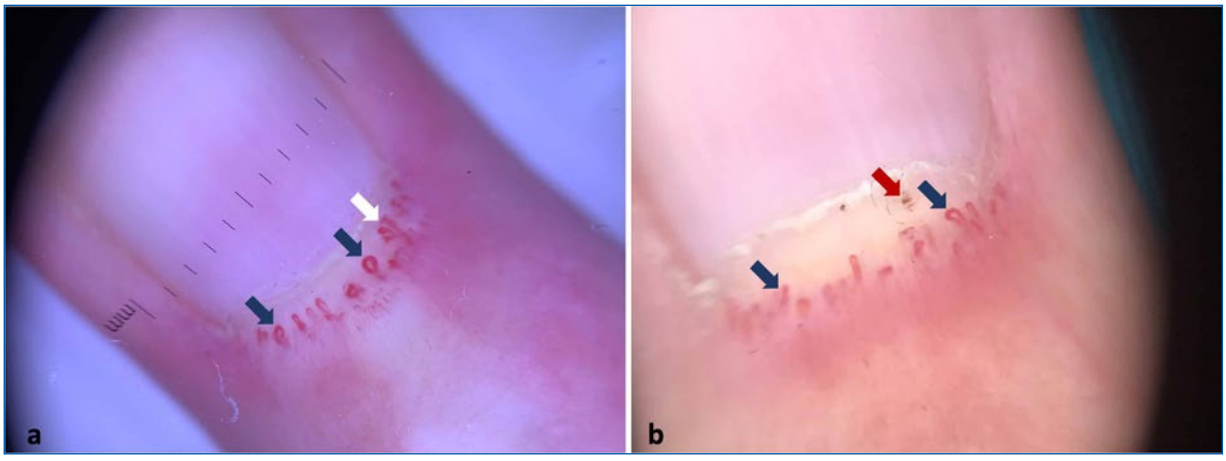

Figure 2. Nailfold capillaroscopy of patient 2 with handheld dermatoscope revealed enlarged capillaries (blue arrows–a, b), ramified capillaries (white arrow–a) and microhemorrhage (red arrow–b). (Dermlite© DL4, x10).

Previous studies have suggested NC as a useful tool for assessing muscular and extra-muscular disease in DM[4,5]. NC abnormalities have been associated with muscle disease activity[4], internal malignancies[4], skin[4] and lung disease[5]. In fact, a retrospective study with 27 patients with interstitial lung disease (ILD) associated with DM, found that microhemorrhage was significantly higher in patients who died due to ILD[5]. The authors also found a correlation between the NC findings and the disease activity indicators of DM-ILD. However, the literature is controversial and other studies failed in achieving association between NC abnormalities and muscular/extra-muscular involvement[2]. Similarly, there isn't enough evidence that capillaroscopy findings allow distinction between ILD and neoplasia associated DM, or between anti-MDA5 and anti-TIF1-γ profiles.

We believe that HD cannot fully replace videocapillaroscopy, since the accuracy for NC abnormalities is lower with the former. However, HD allows a quick

screening of the presence of capillary involvement in DM.

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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LETTER TO THE EDITOR

Extragenital lichen sclerosus with angiokeratoma-like changes

Líquen escleroso extragenital com alterações semelhantes a angioqueratoma

Gabriela F. Melo[1,a], Fabiana B. Coutinho[1,b], Isabelle S.M.T. Ferreira[2,c], and Flauberto S. Marinho[1,d]

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To the Editor:

We present a case demonstrating the possibility of manifestations of extragenital lichen sclerosus (LS) with angiokeratoma-like changes.

A 53-year-old woman developed a pruritic and infiltrated cutaneous lesion near the angle of the left shoulder blade, with sudden and progressive onset. It was a well-delimited plaque measuring 5 × 10 cm, hypochromic but with brownish hyperpigmentation at the periphery, with a marble-like and pearly white appearance and purplish areas on the center (Fig. 1A). Dermoscopy showed fibrotic beams/white clouds, yellow-white follicular plugs, in addition to vascular structures of dotted and comma-like formats (Fig. 1C).

The clinical hypothesis of extragenital LS supported by dermoscopy was further confirmed by histopathology which revealed a rectified and thin epidermis, with orthokeratotic hyperkeratosis and follicular hyperkeratosis, marked vascular ectasia in the superficial dermis with extravasation of red blood cells in the subepidermal region and diffuse sclerosis in the middle and deep dermis (Figure 1D and E), findings compatible with LS-like angiokeratoma.

Treatment with clobetasol propionate 0.05% cream twice a day for 30 days was followed by once at night for a further 30 days, in addition to emollients. Due to relapsing pruritus, treatment with betamethasone dipropionate cream and tacrolimus ointment 0.1% in alternate days was maintained for 6 months, with improvement of pruritus, consistency and texture, and with partial lesional re-pigmentation (Fig. 1B). No other lesions were detected, namely in the genital area, nor any other concomitant pathology.

Lichen sclerosus (LS) affects mainly the anogenital area, but it occurs in the extragenital areas in about 15-20% of cases, most commonly on the thighs, neck, breasts, trunk and back[1] Despite being more frequent in Caucasians[2] and in women between 50 and 60 years[3], its occurrence is independent of age, race and sex[4].

Characteristic lesions are asymptomatic ivory or porcelain-white shiny papules and macules that coalesce to form sclerotic plaques[5]. Diagnosis of LS is usually clinical and can be supported by dermoscopy and, in cases with unusual lesions, by histopathology[6]. Findings suggestive of LS on dermoscopy include areas of erythema, linear irregular red vessels, bright white or white-yellowish patches, yellowish-white keratotic follicular plugs, whitish scaling, hemorrhagic spots, and crystalline structures[7]. Furthermore, as in the present case, vascular structures of different lengths and shapes have also been reported[6].

Most frequent histological findings include hyperkeratosis, epidermal atrophy, hyalinosis, follicular plugging, dermal edema, basal cell vacuolization, and

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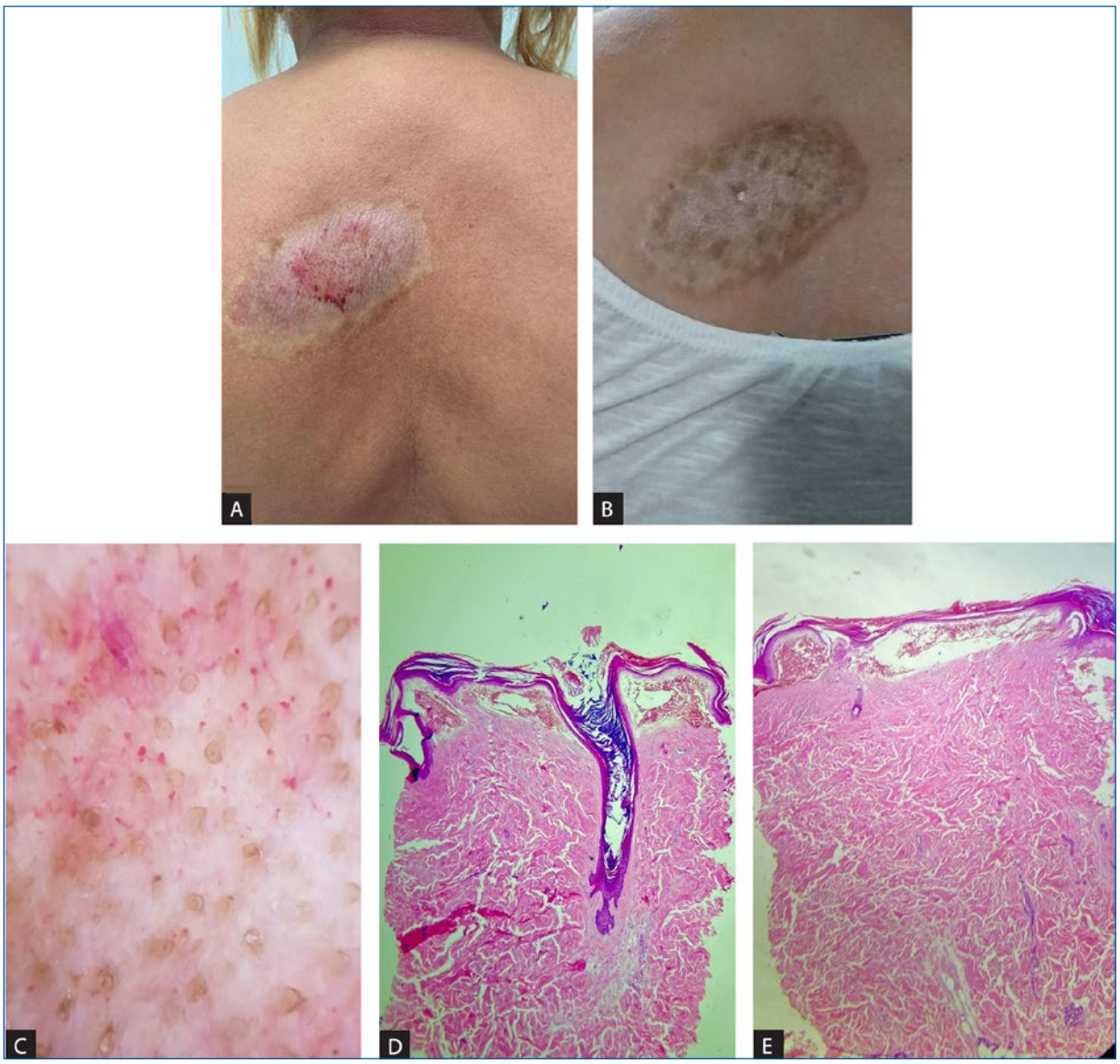

Figure 1. A: a well-delimited hardened, plaque measuring 5 x 10 cm, hypochromic, with a marble-like appearance, pearly white appearance, and purplish areas on the center. **B:** with improved consistency and texture and partial repigmentation after 6 months of treatment. **C:** dermoscopy showing fibrotic beams/white clouds, yellow-white follicular plugs and dotted and comma-like vascular structures. **D and E:** histopathology (H&E, 40x): **D:** rectified and thin epidermis, with orthokeratotic hyperkeratosis and follicular hyperkeratosis and **E:** vascular ectasia in the upper dermis with extravasation of red blood cells and overlying hyperkeratosis.

inflammatory infiltrate[8], but vascular ectasia associated with extravasation of red blood cells in the superficial dermis, similar to angiokeratoma, can also be observed.

Angiokeratomas are superficial vascular ectasias with overlying hyperkeratosis, which manifest as single or multiple red-purple to black nodules. LS can present secondary angiokeratoma-like changes, which are due to the damage caused to the dermis by inflammation. These ectatic thin-walled vascular spaces are observed in the papillary dermis intimately associated with the epidermis[5].

Ethical disclosures

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