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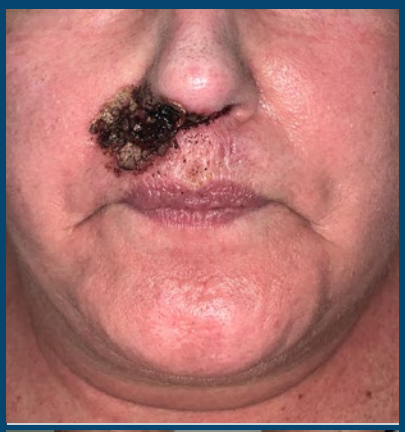

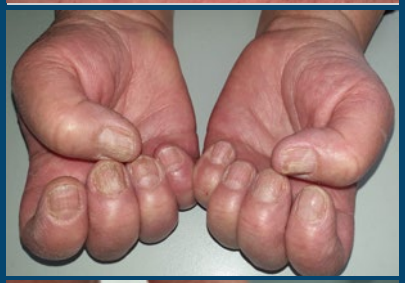

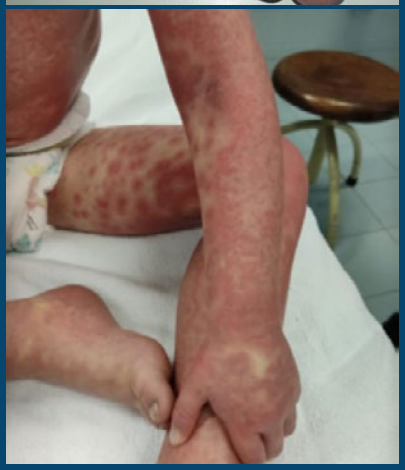

In this issue:

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Cover design: Histopathology of the skin biopsy with a dermal granulomatous reaction, predominantly superficial, with periadnexal and perivascular involvement (H&E ×40). See article by Freitas et al. in this issue.

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REDUÇÃO DA VERMELHIDÃO

APÓS 7 DIAS

VERMELHIDÃO E RUGAS REDUZIDAS; MAIOR LUMINOSIDADE DA TEZ

APÓS 28 DIAS

-33% VERMELHIDÃO(1)

-17% RUGAS(2)

+29% TEZ LUMINOSA(1)

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Anti-inflamatória(4)
Antienvelhecimento(5)

98% DE INGREDIENTES DE ORIGEM NATURAL

22 INGREDIENTES

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* Pele sujeita a vermelhidão e/ou sujeita a tratamentos dermatológicos. 1- Autoavaliação – 22 mulheres – 28 dias – 2 aplicações por dia. 2- Avaliação clínica – 22 mulheres – 28 dias – 2 aplicações por dia. 3- Casares et al., 2020 4 -Petrosino et al., 2018, Gegotek et al., 2019, Sangiovanni et al., 2019 5- Gegotek et al., 2019 Supp et al., 2019.

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ESSENTIAL 3 CERAMIDES

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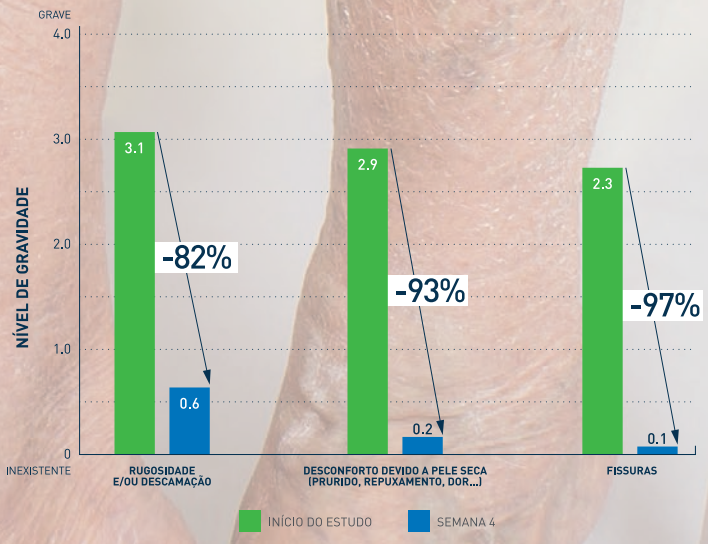
AVALIAÇÃO DERMATOLÓGICA

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



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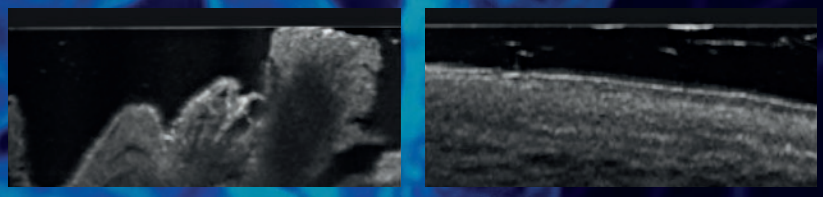
DISPOSITIVO MÉDICO

ANTHELIOS 100 KA+ MED

PREVENÇÃO E PROTEÇÃO
DO DESENVOLVIMENTO
DE QUERATOSE ACTÍNICA
E CANCRO DA PELE
NÃO MELANOMA (NMSC)

EFICÁCIA DEMONSTRADA
EM PELE MUITO FOTOSSENSÍVEL

PREVINE OS DANOS MORFOLÓGICOS DA PELE*.
ESTUDO *IN VITRO*



REPARA AS LESÕES DE QUERATOSE ACTÍNICA**.
ESTUDO *IN VIVO*

+ 50ml | CNP: 7089383

* Observação histológica em pele artificial antes e depois da aplicação de uma fórmula equivalente.
** Tomografía de coerência óptica confocal (LC-OCT). 20 doentes, 50-70 anos com lesões de queratoses actínicas e campo de cancerização. Aplicação de **Anthelios 100 KA+ MED** uma vez/dia, durante 8 semanas. Imagens antes e depois.

LA ROCHE-POSAY. A EXIGÊNCIA DERMATOLÓGICA.

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PSORIASIS SCALP SEVERITY INDEX
(CHAMPÔ+TRATAMENTO)

- Diminuição do eritema
- Diminuição da espessura e dureza das películas
- Diminuição da descamação

82% dos doentes (que já utilizavam medicação tópica) afirmaram que a combinação com o champô testado era **mais eficiente** que outras combinações**.

* Estudo clínico com score e auto-avaliação em 54 indivíduos após 2 semanas de uso diário em combinação com um tratamento de betametasona e calcipotriol.
** Auto-avaliação em 50 indivíduos após 4 semanas de uso diário.

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

Atopic dermatitis: improving patient access to health care in dermatology

Dermatite atópica: melhorar o acesso dos doentes aos cuidados de saúde em dermatologia

Tiago Torres[1,a], Margarida Gonçalo[2], Maria J. Paiva-Lopes[3], Cristina Claro[4], Paulo Varela[5], João M. Silva[6], Ana Cordeiro[7], and Pedro Mendes-Bastos[8]*

[1]Serviço de Dermatologia, Centro Hospitalar Universitario de Santo António, Porto; [2]Serviço de Dermatologia, Centro Hospitalar Universitário de Coimbra (CHUC) e Clinica de Dermatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra; [3]Centro Hospitalar Universitário Lisboa Central (CHULC)–Hospital dos Capuchos e Hospital Dona Estefânia, Nova Medical School-Universidade Nova de Lisboa, Lisbon; [4]Centro Hospitalar de Lisboa Ocidental (CHLO)–Hospital de Egas Moniz, Hospital da Luz de Lisboa, Hospital da Luz de Oeiras, Portugal; [5]Centro Hospitalar de Vila Nova de Gaia/Espinho, Hospital da Lapa, Oporto; [6]Centro Hospitalar de Lisboa Norte (CHLN)–Hospital Santa Maria, Hospital CUF das Descobertas, Clínica CUF Alvalade, Clínica Dermatológica Dr. João Maia Silva; [7]Centro Hospitalar Lisboa Central (CHLC)–Hospital Dona Estefânia, Hospital da Luz da Lisboa; [8]Hospital CUF Descobertas, Centro de Dermatologia de Lisboa, Lisbon, Portugal

[a]ORCID: 0000-0003-0404-0870

Abstract

Introduction and Objective: The present study on atopic dermatitis (AD) in Portugal aims to characterize patient needs and discuss measures to improve health care in dermatology, particularly in cases of moderate to severe disease. **Methods**: The study was conducted in three phases–(1) data collection on the patient access to healthcare and subsequent analysis; (2) critical evaluation of the data in individual interviews with dermatologists and one pediatrician; and lastly, (3) data discussion in consensus meetings to validate the existing care capacity in dermatology, to identify gaps in care for patients with AD and to define mitigation strategies. **Results**: In Portugal, it is estimated that AD affects ~ 360,000 patients, 70,000 of whom have moderate to severe disease. Healthcare capacity analysis confirmed that the private system plays an important role in the management of AD. It is estimated that 30% of patients rely solely on the Portuguese public health service. Nevertheless, patients with moderate to severe disease can only access advanced targeted therapies from public healthcare providers. Analysis of public care capacity in dermatology shows relevant gaps in the referral system, the geographical coverage of specialized centers, the number of specialists and high waiting times for first appointments. Considering the negative impact of the disease on patients' quality of life, 86% of patients with AD use private settings to better manage their disease. **Conclusion**: In conclusion, private setting bridges the gaps in public health care capacity in dermatology, and therefore, it is crucial for patients with AD. However, a major limitation is the lack of reimbursement for advanced targeted therapies recommended for moderate to severe AD when they are prescribed in a private setting, thus compromising patient access to these therapies. A possible strategy could be to extend the prescription of these therapies to a private setting based on a reimbursement model similar to that outlined in Act 48/2016 of 22 March.

Keywords: Health equity. Health services accessibility. Essential drugs. Dermatology. Delivery of health care. Atopic dermatitis.

***Corresponding author:**
Tiago Torres
E-mail: torres.tiago@outlook.com

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Resumo

Introdução e Objetivos: O presente estudo sobre a dermatite atópica em Portugal tem por objetivos a caracterização das necessidades dos doentes e discutir medidas tendentes a melhorar os cuidados de saúde em Dermatologia, particularmente nos casos de doença moderada a grave. **Métodos**: O estudo foi conduzido em 3 fases: 1) recolha de dados sobre o percurso do doente com dermatite atópica em Portugal e subsequente análise; 2) a avaliação dos dados em entrevistas individuais com especialistas de Dermatologia e um de Pediatria; e finalmente, 3) as conclusões foram discutidas em reuniões de consenso para validar a capacidade assistencial existente em Dermatologia, para identificar lacunas nos cuidados dos doentes com dermatite atópica e para definir estratégias de mitigação. **Results**: Em Portugal, estima-se que a dermatite atópica afete ~ 360,000 doentes, dos quais 70,000 têm a doença moderada a grave. A análise da capacidade assistencial confirmou que o sector privado representa um papel importante no acompanhamento e no tratamento da dermatite atópica. Estima-se que apenas 30% dos doentes depende exclusivamente do Serviço Nacional de Saúde. Porém, os doentes com formas moderadas a graves continuam a utilizar os serviços públicos de saúde para aceder a terapêuticas avançadas. A análise da capacidade assistencial pública em Dermatologia demonstrou lacunas relevantes no sistema de referenciação, cobertura geográfica de centros de especialidade e número de especialistas, bem como elevados tempos de espera para primeiras consultas. Considerando o impacto negativo da doença na qualidade de vida dos doentes, 86% dos doentes com dermatite atópica recorrem ao setor privado para melhor gerir a sua doença. **Conclusões**: Em conclusão, o sector privado poderia complementar as lacunas da capacidade de cuidados públicos de saúde em Dermatologia, algo que é crucial para os doentes com dermatite atópica. Contudo, na prática, isto não é possível pela inexistência de um regime de comparticipação para terapêuticas avançadas para esta doença no sector privado, comprometendo assim o acesso dos doentes a estas terapêuticas. Uma possível estratégia poderia ser o alargamento da prescrição de terapêuticas avançadas ao sector privado, tendo por base um modelo de comparticipação semelhante ao delineado pela Portaria nº48/2016, de 22 de março.

Palavras-chave: Dermatite atópica. Dermatologia. Prestação integrada de cuidados de saúde. equidade Em saúde. Medicamentos essenciais.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by itching, skin dryness with scaling, erythema, edema, vesiculation, fissuring, and lichenification[1]. Disease severity is classified as mild, moderate, or severe, depending on the percentage of body area affected, the severity of signs and symptoms, and disease evolution[2]. Moderate to severe AD has a major negative impact on quality of life. In a study carried out in Portugal, 36% of patients with AD reported that their disease had a very significant or extremely significant impact on their lives[3]. These patients often have sleep disorders (34% of patients), anxiety, and depression, reporting disease aggravation after performing simple daily tasks such as bathing or playing sports[3–5]. In addition to its impact on quality of life, moderate to severe AD has high costs associated with lost productivity (absenteeism and presenteeism). In a situation similar to that of Portugal, in Spain, it is estimated that AD results in a loss of working days in 24.5% of cases[6]. This translates into an economic cost of €1057 per patient per year in severe forms of the disease, €538 per patient per year in the moderate forms, and €196 per patient per year in the mild forms[6].

Since AD is a chronic disease that cannot be cured, its treatment involves strategies and therapies focused on minimizing the impact of the disease-associated symptoms. First-line therapy in patients with mild disease consists of general measures (including the daily use of emollients), topical corticosteroids, and/or topical calcineurin inhibitors[7]. In addition to these therapies, moderate to severe AD may require systemic therapies, such as ciclosporin, methotrexate, and oral corticosteroids, or other therapeutic alternatives, such as phototherapy, which can have significant adverse effects[7]. More recently, innovative therapies have been developed, including biological medicines and oral small-molecule drugs, which have revolutionized the treatment of this disease[8,9]. These have fewer adverse effects, resulting in an improvement in the patient's quality of life, as well as an improvement in work and/or school productivity due to better management of the disease (fewer symptoms and fewer adverse effects).

Patients with mild disease are mostly followed up in primary care by their general practitioner/family doctor within the Portuguese National Health Service (Sistema Nacional de Saude - SNS), whereas the majority of patients with moderate to severe AD are followed up in specialized medical care, mostly in dermatology. Due to the high impact on patients' quality of life, the dermatology capacity is critical and decisive in the disease management of AD patients[9,10].

Table 1. Dimensions of analysis, metrics, and criteria

Dimensions of analysis	Metrics characterization and sources	Criteria
Epidemiology	Prevalence (%)[11-16]	Percentage in Portugal or comparable countries Resident population in Portugal[11] According to the age ranges: Children (< 12 years old) Teenagers (12-17 years old) Adults (> 18 years old)
	Incidence (%)[17]	
Analysis of capacity of dermatology care services in Portugal	Demand for AD health care services[3]	Specialty: Dermatology National Continental Territory[23]
	Referring patients to the National Health Service	
	Annual production in dermatology[18]	
	Territorial coverage of dermatology[18-20]	
	Waiting time for a first consultation[21,22]	
Quality of life and care needs	Symptoms on quality of life[3]	Patients with AD (includes patients with moderate to severe disease)
	Reasons for AD patients use of the private care system[3]	

AD: atopic dermatitis.

Table 2. Consensus meeting script

Prevalence	What is the best estimation for prevalence of AD in Portugal? And in moderate to severe disease?
Health care needs	What is the best estimation for appointment needs in patients with moderate to severe AD?
Access barriers	What are the key barriers that affect the access of these patients to specialty care (in dermatology)?
Strategies and solutions	What are the possible strategies to improve access to advanced therapies in private sector? What are the other possible strategies?

The main objective of this study is to characterize the current care capacity in dermatology (in both public and private settings), to assess its suitability to the needs of patients with moderate to severe AD, and to identify potential strategies to improve health care provided to these patients. This study explores the capacity of dermatology care in Portugal for patients with moderate to severe AD. It highlights patient needs and the obstacles and limitations facing the current service provision.The information and data for this study were reviewed by a group of experts in individual meetings. Finally, a consensus meeting was held with a panel of experts to discuss all the topics addressed and possible strategies or solutions to mitigate the main problems, particularly the use of the Portuguese public health service (SNS) or private setting for dermatology appointments. A final result is a comprehensive approach which enables better care provision to patients with moderate to severe AD in Portugal regardless of whether they are managed in the SNS or private setting.

Materials and methods

The analysis was conducted in three stages: (1) data collection; (2) individual interviews to validate the information; and (3) two consensus meetings with a panel of experts.

The literature review focused on analyzing the epidemiology of AD in Portugal, health care capacity in dermatology, impact on quality of life, and patients' care needs, centering on patients with moderate to severe disease. The panel of experts included seven dermatologists and one pediatrician (with multidisciplinary experience in pediatric AD management), who were selected based on their experience in AD management, geographic distribution, private or public clinical practice, and their participation in publications related to AD in Portugal. The interview stage took place in September 2021 and comprised eight individual remote interviews. The aim was to validate data and identify additional relevant data sources (Table 1). The validated information was used to support a structured discussion at the

Table 3. Prevalence of AD patients per age in Portugal

	Resident population	Prevalence of AD	Patients with AD	Patients with AD moderate to severe	
Children (≤ 12 years)	990,836[11]	(11.0-15.5%)[12]	108 992-153 580	20.0%[16]	21,798-30,716
Teenagers (12-17 years)	617,281[11]	(8.0%-9.0%)[13]	49 382-55 555	33.0%[15]	16,296-18,333
Adults (≥ 18 years)	8,759,648[11]	(0.61%-2.64%)[14]	53 434-231 255	33.0%[15]	17,633-76,314
Total	-	-	211 808-440 390	-	55,727-125,363

AD: atopic dermatitis.

consensus meetings held in January 2022 (Table 2). At this meeting, an agreement was reached on the epidemiology of AD in Portugal, the healthcare needs of these patients, and the current capacity of dermatology to support AD management. Based on the general agreement, the panel of experts discussed and agreed on potential strategies to address the current gaps in health care for AD.

Results

To characterize the dermatology capacity in Portugal for AD patients, several dimensions were analyzed, including those related to AD epidemiology, estimated demand in public and private health care services, existing referral processes to access specialty care on the public health service, annual production in dermatology in the public sector, territorial coverage of public and private dermatology services and waiting times for a first appointment in dermatology in a public setting, and finally the impact of AD on patient quality of life and their needs.

Epidemiology

There are no studies evaluating the real prevalence of AD in Portugal but based on data from neighboring countries and expert consensus, there were estimated to be approximately 360,000 patients in Portugal (Table 3). This equates to approximately 3.5% of the population. The prevalence of AD varies significantly across age groups (≤ 12 years old, 13-17 years old, ≥ 18 years old), with estimations in the Portuguese population shown in Table 3. In Portugal, 20% of AD patients have moderate to severe disease[16], which represents an estimated 70,000 individuals.

Additionally, AD incidence in patients < 18 years old is expected to continue growing. Epidemiologic studies between 1990 and 2010 in several European countries showed an increasing trend in AD[17]. Experts have justified these figures based on the increasing AD-associated risk factors, such as a more urban lifestyle, increased exposure to environmental pollution and other factors, such as hygiene habits, high stress, diet, etc.

Increasing numbers of AD patients and a greater awareness of the disease, and the need for treatment are placing more pressure on the SNS to keep up with the growing number of patients.

Analysis of the capacity of dermatology care services in Portugal

Demand for AD health care services in the public and private sector–most AD patients are followed and manage their disease in private settings, with only approximately 30% of patients being treated exclusively in public settings[3]. Typically, patients with moderate AD learn to manage their disease on their own, requiring fewer medical appointments. These patients are often followed in primary care in the public sector. In contrast, patients with moderate to severe disease need specialized care and more regular follow-up, relying on both public and private settings. In Portugal, the percentage of patients treated exclusively in private settings seems to decrease as disease severity increases[3].

Experts agree that patients need to have regular appointments and access to advanced therapies. Patients with moderate to severe diseases that require advanced therapies are referred to public consultations to guarantee their access to treatment.

Referring patients to the SNS–access to advanced therapies is thus the main reason identified by the experts for referring patients with moderate to severe AD from private settings to the SNS. Experts analyzed the

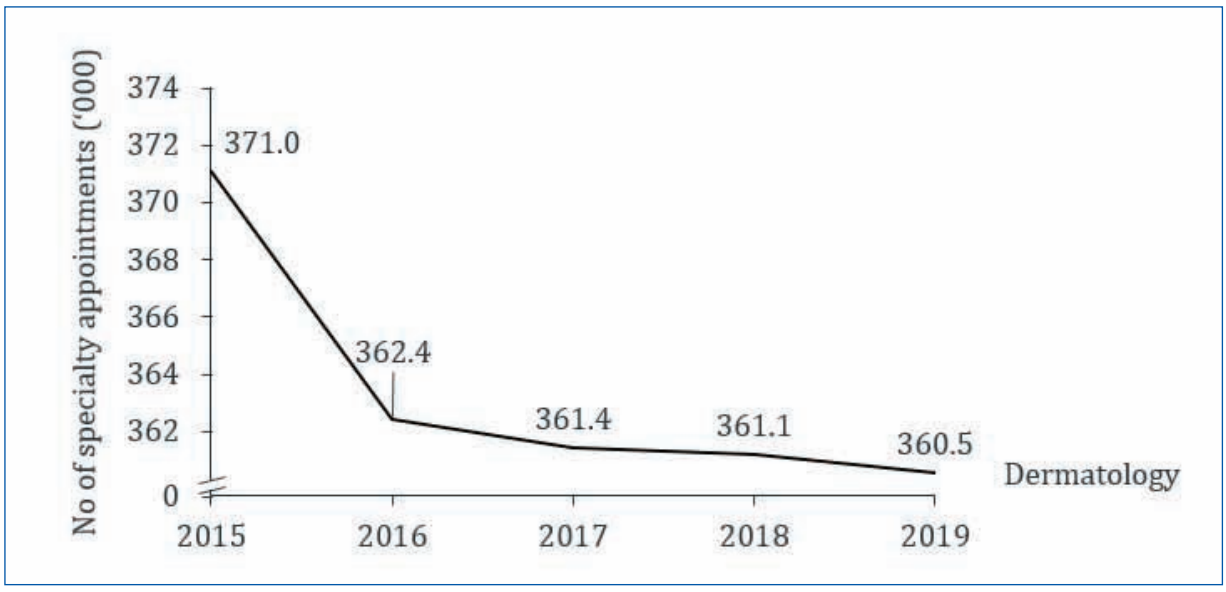

Figure 1. Evolution of production of specialties in dermatology in public health care (2015–2019, all diseases)[18].

current referral process to public dermatology consultations and identified major limitations. In hospital triage upon referral to dermatology, moderate to severe AD is not classified as a "priority" or "high priority" disease in adults, leading to longer waiting times for a first consultation. Secondly, dermatology in public care includes the monitoring of patients with suspected oncologic cases, and therefore, AD patients have a relatively lower priority. Finally, this process often depends on the referral from public primary care to specialized care. Considering the low coverage of family doctors in primary care, AD patients often have limited access to dermatology care if not from private referral. To illustrate the issue, about 9 and 44% of doctors in general practice are between 61 and 65 and > 65 years of age, respectively[23]. Therefore, access to primary care is expected to worsen rapidly.

Annual production in dermatology–the number of dermatology consultations on the SNS decreased by 2.3% between 2015 and 2019 (–0.2% between 2018 and 2019)[18]. Considering the experts' predictions, mild AD patients require between one and two dermatology consultations per year, while patients with moderate to severe AD require three to four per year. Therefore, in Portugal, moderate to severe AD requires an estimated 245,000 consultations per year (70,000 patients requiring ~ 3.5 consultations/year), which represents about 68% of existing[18] public dermatology production. Therefore, the experts consulted agreed on the importance of the private sector in complementing the existing public dermatology production (Fig. 1).

The territorial coverage of dermatology (institutions and specialists)–There are significant regional differences in the distribution of providers of dermatologic care, both in the SNS and private sectors. Private setting plays an essential role in complementing the SNS, namely mitigating the regional differences in coverage. Figures 2 and 3[18-20] illustrate the uneven territorial distribution in dermatology centers and specialists, respectively. When compared, the North and Center regions and the region of Lisbon have more resources in specialized care in dermatology than the southern regions. Reduced public coverage by centers specialized in dermatology was found in the Alentejo and the Algarve; some districts did not have public dermatology care services. Considering the territorial coverage of dermatologists, it is insufficient to meet the recommended ratio of 1/30,000-35,000 dermatologists for the population covered[20].

This asymmetry reflects in poorer access to this specialty care by patients with AD. As a result, they are forced to travel longer distances to dermatology consultations, hampering disease management and equating to costs for patients and society as a result of higher absenteeism. The experts consulted indicated that private healthcare providers could play a key role in complementing the gaps in public dermatology capacity. However, this is not yet possible since physicians in private settings have a more limited therapeutic arsenal.

Waiting time for a first consultation–dermatology is one of the specialties that have the greatest difficulties in

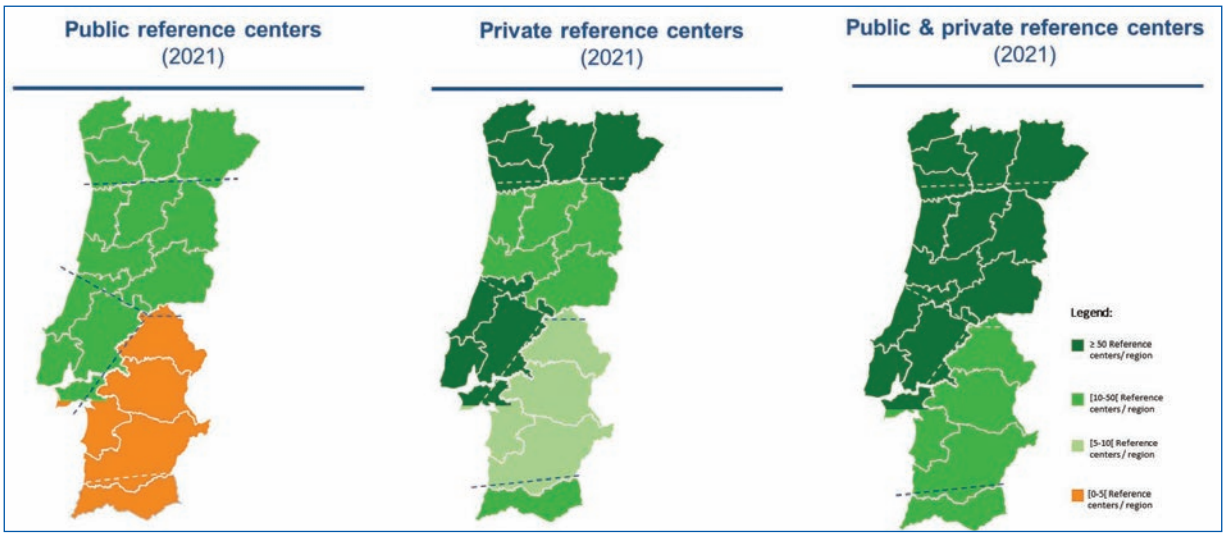

Figure 2. National coverage of specialty centers in public and private sector[19,20].

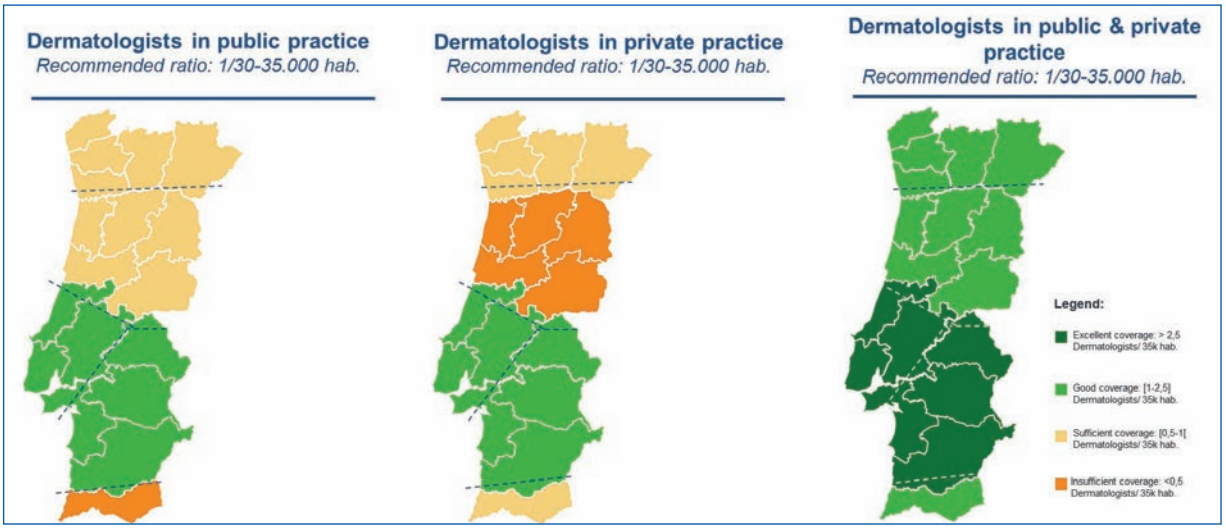

Figure 3. National coverage of dermatologists in public and private sector[19,20].

complying with the maximum guaranteed response time (MGRT) for first face-to-face consultations. In 2019, this goal was met in 51% of cases[23]. In the case of dermatology telescreening, the response time is ~ 70%[19]. The same trend can be found in performance data for previous years, such as 2018 in public dermatology care services[24].

Additionally, dermatology patients classified as "normal" priority waited for an average of 236 days (9 months)[21], while the maximum stipulated response time was 120 days[22]. Patients with a "priority" or "high priority" classification waited on average 40 days[21], compared to the maximum response time of 60 days and 30 days, respectively[22]. A comparison with patient-reported data reveals that in private settings, patients waited on average 14 days for dermatology appointments[3].

From the experts' experience, AD patients are usually assigned a "normal" priority at hospital triage, even in moderate and severe cases. Moreover, experts considered that the 60-day waiting time established in the MGRT for a "priority" case could still be considered long for patients with more severe diseases.

The experts consulted believed the average 236 days waiting time for "normal" priority would result in the absence of adequate treatment due to lack of specialist assessment and may lead to a significant reduction in the quality of life of these patients, given the chronic and recurring nature of the disease, characterized by repeated cycles of exacerbation and improvement. In the absence of treatment in moderate to severe cases, patients remain in a serious clinical state until receiving specialized care.

Episodes of AD exacerbation are one of the main reasons why patients with moderate to severe AD go to the emergency room more often and opt for private care (21-35% of patients)[3].

Quality of life and care needs

It is reported that moderate to severe AD affects patients' quality of life significantly, with 34% of patients reporting sleep disorders, 33% anxiety, 27% difficulties in bathing, 19% difficulties in dressing and undressing, and 5.2% depression[3]. A total of 86% prefer private care as a result of shorter waiting times, and 49% prefer private care because of the possibility of choosing a specialist[3]. Moreover, from the experts' experience, patients also resort to private care due to greater flexibility in scheduling appointments outside working hours and based on geographic proximity.

Discussion

The results of the present study demonstrate that there are significant gaps in the management of patients with AD in Portuguese public health care. These gaps are of particular importance in moderate to severe cases of AD and include:

- Limitations in the existing referral of adult patients with AD to dermatology consultations in the public services.
- Territorial coverage of dermatology centers in the public service, with significant regional differences.
- Insufficient coverage of dermatologists in the public service to meet the recommended ratios.
- Long waiting times for first consultations in dermatology on the public service.

Considering the above limitations, it is of the greatest importance to define strategies that ensure AD patients can have access to continuous monitoring and treatment through a truly complementary healthcare network in dermatology, covering both public and private institutions. In this regard, equal access to advanced and innovative therapies for AD patients is the area in which private dermatology health care cannot truly complement the public health care system.

Special reimbursement and prescription regimens for innovative advanced therapies in the private health care system already exist in the Portuguese public health service, but they do not cover AD. One of the most innovative approaches was the development of Act 48/2016 on 22 March. This legislation provided the legal framework to support patients with conditions that have a high impact on their quality of life, such as plaque psoriasis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and polyarticular juvenile idiopathic arthritis. This law enabled them to have access to innovative advanced therapies, regardless of the setting in which the patient was being treated.

A possible approach to improve AD patients' access to advanced therapies, such as biological agents and small molecules, could be the extension of Act 48/2016 of 22 March to include AD. An alternative approach could be the creation of a similar new legal framework covering AD, recognizing specific features in the reimbursement and dispensing advanced therapies approved for the treatment of this condition. In this case, the competent authorities would have to define under which conditions these therapies would be available, as well as balance the severity of the disease with its impact on the patient's quality of life.

These legal measures are likely to result in a positive impact by:

- Minimizing the impact of long waiting times on the quality of life of patients with moderate to severe AD.
- Eliminating barriers and inequalities of access, promoting patient access to similar therapeutic options regardless of being treated in public or private health care, in accordance with the provisions of Act 99/2022 (Article 3-A)[25]. With this legal framework, the inclusion of AD in a special prescription regimen becomes even more urgent, as it becomes the responsibility of the hospital's Pharmacy and Therapeutics Committee to define and approve protocols determining the criteria and conditions of use for these medicines, enabling the rigorous evaluation of these criteria according to the context and needs of the population.

Reducing the referral of patients managed in the private sector to dermatology consultations in the public health service, which is mainly justified to enable access to innovative therapies such as biological agents and small molecules.

Although this framework mitigates considerable limitations and barriers in public health care, particularly for patients with moderate to severe AD, the expert panel believed that strict dispensing criteria should be anticipated for the prescribing centers duly registered at the Directorate-General for Health, meeting national and international best practices for dispensing advanced therapies. These could be defined or revised by a group of experts, specialists, or medical societies selected on the basis of their high-level experience in this type of therapy.

Conclusion

This study analyzed the epidemiology of AD in Portugal and the current capacity of public and private dermatology care services to meet patient needs. The analysis addressed the use of public and private health care services by patients with AD, the adequacy of the referral process, which is essential to gain access to advanced target therapies, the capacity of the public dermatology services to manage the Portuguese population with AD, the differences in territorial coverage according to dermatologists and clinical centers in the public and private sectors and, finally, the waiting times to be treated with advanced target therapies. The results showed significant limitations and barriers to addressing patient needs, as well as important regional asymmetries.

The importance of continuous monitoring and treatment of patients with moderate to severe AD is critical to the management of this chronic disease.

In conclusion, we make recommendations to ensure continuity of care and equal care for patients with moderate to severe AD by their physicians, regardless of the setting. This would promote trust in the physician-patient relationship and improve adherence to therapies that prevent the progression of AD into more severe forms, which in turn translates into higher future costs and poor quality of life.

As a final remark, it is vital to respect a patient's freedom of choice to be cared for by a specific healthcare professional of their choice. There is also insufficient justification for preventing eligible patients with moderate to severe AD from accessing innovative therapies in a timely way so as to avoid disease progression.

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Conflicts of interest

Tiago Torres: AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz, and UCB; Margarida Gonçalo: has collaborated in advisory boards and/or lectures for Abbvie, Astra-Zeneca, Leo, Lilly, Pfizer, Novartis, Sanofi, Takeda; Maria J. Paiva-Lopes: AbbVie, Almirall, Boehringer Ingelheim, Janssen, Leo-Pharma, Eli Lilly, Novartis, Pfizer, Sanofi-Genzyme, Viatris; Cristina Claro: speaker in events for Johnson & Johnson, Galderma, Mylan, Ferrer, Leo and Sanofi and Advisory Board team member of Sanofi, Leo, Johnson & Johnson and Ferrer; Paulo Varela: Abbvie, Almirall, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Galderma, Isdin, Janssen-Cilag, Leo, Lilly, Medinfar, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Sanofi; João M. Silva: no conflicts of interest; Ana Cordeiro: no conflicts of interest; Pedro Mendes-Bastos: Speaker, consultant or advisor for AbbVie, Pfizer, Janssen-Cilag, Leo-Pharma, Novartis, Eli-Lilly, Sanofi, Teva, L'Oreal, Pierre Fabre, Cantabria Labs, Organon, Viatris, Eveloe CS Laboratorios and Principal investigator in clinical trials supported byAbbVie, Janssen, Novartis, Pfizer e Sanofi.

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.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Neutrophil/lymphocyte ratio as serum inflammatory biomarker in patients with moderate-to-severe plaque psoriasis

Razão neutrófilo linfócito como marcador inflamatório sérico em pacientes com psoríase vulgar moderada-grave

Maria E. Agapito-Valgas[1], Lara J. Justo-Silva[2,3], Fraciele Cascaes da Silva[4,5], Fabiana Oenning-da-Gama[1], Gustavo Moreira-Amorim[6,7], and Sueli Carneiro[8,9]*

[1]University of Southern Santa Catarina (UNISUL), Santa Catarina; [2]Federal University of Santa Catarina, Florianópolis; [3]Dermatology Service, Hospital Santa Teresa-SES/SC, Rio de Janeiro; [4]University of Southern Santa Catarina (UNISUL), Florianópolis; [5]Educational Society of Santa Catarina University (UNISOCIESC); [6]University of Southern Santa Catarina (UNISUL), Florianópolis; [7]Department of Dermatology, Hospital Santa Teresa-SES/SC, Santa Catarina; [8]Department of Dermatology, State University of Rio de Janeiro, Rio de Janeiro; [9]Department of Pathological Anatomy, Faculdade de Medicina da UFRJ, Rio de Janeiro, Brazil

Abstract

Introduction: Psoriasis is an immune-mediated, chronic, inflammatory, systemic disease that primarily affects the skin and joints. Despite advances in the comprehension of the disease, there is still a lack of biomarkers available for clinical use. **Objective:** To evaluate neutrophil-lymphocyte ratio (NLR) as a marker of systemic inflammatory status in patients with moderate to severe plaque psoriasis vulgaris, compared with controls. **Methods**: Observational case-control study, conducted in a public hospital unit, focused on skin disease. A total of 165 patients with psoriasis and 187 healthy subjects seen between August and December 2020 were studied. **Results:** The group of cases showed a greater median of NLR compared with controls (medium = 1.96, p = 0.032). When stratified by age, the median NLR was higher in individuals between 31 and 60 years, with statistical significance. No differences were identified in gender, presence of arthritis or comorbidities. **Study limitations**: Observational, retrospective, single-center study based on medical records review. **Conclusion:** NLR was higher in individuals with psoriasis when compared with controls. It is simple, inexpensive and available in all levels of care, based on an elementary laboratory test that is already part of the routine care of patients with psoriasis. Its use in evaluating systemic inflammation could contribute to better management of psoriatic disease.

Keywords: Psoriasis. Neutrophils. Lymphocytes. Autoimmune disease.

Resumo

Introdução: A Psoríase é uma doença crônica, inflamatória, imunomediada, sistêmica, com especial predileção pela pele e pelas articulações. Apesar dos avanços em seu entendimento, faltam biomarcadores laboratoriais para uso clínico. **Objetivo:** Determinar a diferença na razão neutrófilo/linfócito (RNL), como marcador inflamatório sérico, entre pacientes com psoríase vulgar moderada quando comparados a indivíduos sem psoríase. **Métodos:** Estudo observacional, tipo caso-controle, realizado em uma unidade hospitalar e ambulatorial pública de atendimento a pacientes com doenças dermatológicas. Fizeram parte do estudo os pacientes com psoríase (165 casos) e controles sem psoríase (187) atendidos no local, entre agosto de 2018 a dezembro de 2020. **Resultados:** O grupo dos casos apresentou maior mediana de RNL em relação aos controles (md = 1,96,

***Corresponding author:**
Gustavo Moreira-Amorim
E-mail: gustavomoreiraamorim@hotmail.com

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p = 0,032). Não houve diferença quanto ao gênero ou presença ou não de comorbidades. Verificou-se, no entanto, quando estratificados por idade, também maior mediana entre casos com 30 e 60 anos, novamente com significância estatística. Não houve diferença entre RNL de pacientes portadores de psoríase, com ou sem artrite. **Limitações do estudo:** Estudo observacional, retrospectivo, unicêntrico, baseado em revisão de prontuários. **Conclusão:** A RNL foi mais elevada em doentes com psoríase em comparação com o grupo controle no presente estudo, de forma similar a outros estudos no assunto. Sugere-se que a RNL possa ser utilizada na avaliação de inflamação sérica destes pacientes, podendo contribuir na condução, manejo e orientação dos pacientes. Constitui marcador simples, acessível em todos os níveis de saúde, cujo exame elementar já faz parte da rotina de cuidado do paciente com psoríase. Hipótese esta a ser testada e corroborada por estudos prospectivos.

Descritores: Psoríase. Doença autoimune. Neutrófilos. Linfócitos.

Background

Psoriasis is an immune-mediated, chronic, systemic, inflammatory disease which primarily affects the skin and joints. There is no difference in prevalence between gender. A bimodal age of onset has been recognized: the first presentation between 16 and 22 years, and a second peak occurring at 57-60 years of age[1-3].

Psoriatic disease is associated with physical and psychological harm, besides substantial negative effects on a patient's quality of life[1,4].

The cutaneous disease usually presents with erythematous and scaly lesions, but the clinical presentation can vary. Psoriasis vulgaris, also called plaque-type psoriasis, which is the subject of this study, is the most common type of psoriasis, which affects 85% of patients. It typically presents as well-defined erythematous plaques covered with wide silvery scales, most commonly over extensors of extremities, back, and scalp[1-3].

The world's prevalence of psoriasis varies between 0.09 and 11.4%, depending on race and geographic site[5,6]. In Brazil, a national telephonic survey found a prevalence of 1.31%[7].

Psoriasis seems to be determined by an inadequate immune response, influenced by genetic factors associated with a predisposition to the development of the disease and some environmental factors that act as triggers or aggravating factors[8-10]. In chronic inflammatory diseases, it is common to search for biomarkers that can be used to interpret each patient's clinical context, contributing to the diagnosis, evaluation of severity or particular phenotype, or identifying inflammatory activity. The NLR is obtained by dividing the total amount of neutrophils by the number of lymphocytes, and it has been studied as a serum marker of systemic inflammatory activity. In this regard, understanding the behavior of these two groups of cells in patients with psoriasis could be useful in helping interpret the different phenotypes inside the clinical spectrum, making therapeutic decisions, and, eventually, revealing potential new targets for treatment[11].

Therefore, the present study aims to determine the NLR as a serum inflammatory marker in patients with moderate to severe plaque psoriasis, compared with controls.

Methods

An observational, retrospective case-control study comparing a cohort of adult patients with severe psoriasis followed in an outpatient clinic of reference in Dermatology.

The cases included patients of both genders, aged 18-80, observed between August and December 2020, who were diagnosed with moderate to severe plaque psoriasis. All cases were diagnosed by the same dermatologist, using clinical criteria[1,12,13] and in a few cases with a less atypical presentation, the diagnosis was supported by a histopathological exam. Patients with synthetic or biological disease-modifying antirheumatic drugs (DMARD) or phototherapy stopped treatment for at least 3 months at the time of blood collection for laboratory examination. The use of topical treatment was admitted. Patients with other autoimmune inflammatory comorbidities were excluded from the study.

Cases were classified as moderate to severe disease when body surface area (BSA) ≥ 10% and/or psoriasis area and severity index (PASI) ≥ 10% and/or dermatology life quality index (DLQI) ≥ 10[13]. Psoriatic arthritis was defined according to CASPAR criteria[14].

The control group included adult patients aged between 18 and 80 years old who were seen at the outpatient clinic.

Cases and controls were matched by sex and age. The sample size was calculated using a 5% of significance level and 80% of statistical power, with a 1:1 proportion ratio, based on values of serum NLR in patients with moderate to severe psoriasis and without psoriasis in a study by Karabay et al.[15]. Considerable differences should be achieved with 165 cases and 165 controls.

Data were obtained retrospectively by reviewing medical records of patients aged between 18 and 80 years old,

Table 1. Clinical and epidemiological characteristics of the group of psoriatic patients and the control group

Variables	Psoriasis patients (n = 165)		Controls (n = 187)	
	n	%	n	%
Sex				
Female	91	55.2	146	78.1
Male	74	44.8	41	21.9
Age group				
≤ 30 years	20	12.1	12	6.4
> 31-60 years	116	70.3	88	47.1
> 60 years	29	17.6	87	46.5
Comorbidities				
Yes	125	75.8	140	74.9
No	40	24.2	47	25.1
Obesity	54	33.8	140	74.9
Hypertension	68	42.5	54	28.9
Diabetes mellitus	36	22.5	103	55.1
Dyslipidemia	37	23.1	54	28.9
Metabolic syndrome	47	29.4	-	-
Fatty liver	28	17.5	69	36.9
Heart disease	13	8.1	69	36.9
Depression/anxiety	41	25.6	-	-
Smoking	52	32.5	26	13.9
Psoriatic arthritis				
Yes	89	53.9	-	-
No	76	46.1	-	-
Use of DMARD*				
Yes	150	90.9	-	-
No	15	9.1	-	-

*Disease-modifying antirheumatic drugs.

observed between August 2018 and December 2020. The NLR serum level was considered the dependent variable. Independent variables studied were age, gendter, presence of psoriasis and psoriatic arthritis and comorbidities.

Data were organized with Windows Excel and analyzed using the Statistical Package for the Social Sciences (SPSS). Version 20.0. (Computer program). Chicago: SPSS Inc; 2009, with the non-normal distribution of data evaluated by Kolmogorov–Smirnov test. The comparison between the case and the control's RNL was performed using the Mann–Whitney *U* test, adopting a significance level of $p \leq 0.05$.

The study was conducted according to the guidelines of Resolution no 466/2012 of the National Health Council, approved by the Ethics Committee of the University of South of Santa Catarina under CAAE np 40169120.4.0000.5369.

Table 2. Anthropometric data and mean psoriasis severity scores of patients

Anthropometric data	Mean (standard deviation)
BMI (kg/m^2)	28.52 (5.18)
AC (cm)	96.10 (12.82)
Psoriasis severity	
BSA	21.23 (13.47)
PASI	18.33 (20.71)
DLQI	13.94 (5.33)

BMI: body mass index; AC: abdominal circumference; BSA: body surface area; PASI: psoriasis area and severity index; DLQI: dermatology life quality index.

Results

A total of 165 patients with psoriasis vulgaris and 187 controls were included in the study. Clinical and epidemiological characteristics are detailed in Table 1.

Table 3. Comparison of median NLR serum levels between cases and controls according to demographic and clinical characteristics

Variables	Patients Median 1.96	Controls Median 1.78	p-value 0.032
Sex			
Male	2.04	1.79	0.227
Female	1.90	1.77	0.400
Age group			
≤ 30 years	1.57	1.59	0.954
> 31-60 years	2.03	1.69	0.022
> 60 years	1.97	1.93	0.669
Comorbidities			
Yes	2.08	1.77	0.054
No	1.77	1.75	0.968

Table 4. Comparison of median NLR serum levels between cases according to the presence of psoriatic arthritis

Psoriatic arthritis	NLR	p-value
Yes	2.08	0.957
No	1.94	-

Anthropometric data and mean psoriasis severity scores are presented in Table 2.

A statistically significant difference was observed (U = 13387.500; p = 0.032) in the NLR between cases and controls, and the case group had a higher median NLR serum level (md = 1.96). Table 3 compares median NLR serum levels between the two groups according to demographic and clinical characteristics.

The present study did not find a statistically significant relationship between NLR and the PASI score (stratifying in patients with PASI ≥ 10 and < 15 vs PASI ≥ 15).

Table 4 demonstrates that there was no difference in NLR between patients with and without psoriatic arthritis.

Discussion

The present study set out to test the NLR as a tool to assess the persistent systemic inflammatory status by comparing patients with psoriasis vulgaris and individuals without psoriasis.

Several inflammation markers have been used to assess the inflammatory state in psoriasis. Acute-phase inflammatory markers, such as erythrocyte sedimentation rate and ultrasensitive C-reactive protein, showed little clinical correlation with the severity of psoriasis vulgaris and were not always related to the presence or absence of joint disease. NLR has been studied in several settings, including psoriasis. In the present study, a higher median was demonstrated in psoriatic cases compared to controls, and this difference was statistically significant when evaluated separately. This finding becomes particularly remarkable once we observe a high prevalence of metabolic and cardiovascular comorbidities in the control group.

When correlated with gender and the presence or absence of comorbidities, the associations were not significant. When divided by age, psoriatic patients aged between 30 and 60 years old had a statistically significantly higher median of serum NLR levels (md = 2.03) compared to controls (p = 0.022), perhaps due to a more significant inflammatory repercussion among younger patients. However, it cannot be ruled out that such a difference was established merely by a greater representation of this age group (70.3% of cases).

In agreement with our findings, a study conducted by Kim et al.[16] also found that patients with psoriasis had increased mean NLR compared to the control group, despite similar total lymphocyte counts. Similarly, Karaby et al.[14] reinforce the association between higher NLR and psoriasis, again with statistical significance.

In addition, another study by Sen et al.[11] demonstrated not only higher NLR but also significantly higher neutrophil counts, in contrast with lower lymphocyte counts, among patients with psoriasis, compared to controls.

Table 5. Summary of NLR studies included in our review.

Authors and year	Methods	n	Results	Author's comments
Sen et al. 2014[11]	Cross-sectional, age and sex-matched controls	138 Pso × 120 controls	Significantly higher neutrophil and lower lymphocyte count NLR levels significantly higher in psoriasis (2.71 ± 1.25 vs 1.90 ± 1.07 p = 0.01). Positive correlation with PASI (PASI < 10: 2.32 ± 1.21 vs PASI ≥ 10 e < 20: 2.61 ± 1.28 vs PASI ≥ 20: 3.42 ± 1.05 p < 0.01).	NLR is a simple, inexpensive and easily assessable marker of systemic inflammation in patients with psoriasis.
Ataseven et al. 2014[18]	Case-control	104 Pso × 70 controls	NLR significantly elevated in (2.19 ± 1,11 vs 1.80 ± 0.72; p < 0.01). No correlation with PASI.	NLR as an emerging marker of inflammation and psoriasis.
Kim et al. 2015[16]	Case-control	111 Pso (25 PsA) × 94 controls	NLR significantly higher among PsA compared with Pso and controls (2.95 ± 1.16 vs 2.15 ± 1.65 vs 1.76 ± 0.89; p < 0.0001); NLR correlated positively with PASI (higher NLR in PASI ≥ 10).	NLR as a strong predictor of PsA (OR 3.351; 95% confidence interval 1.785–6.292; p = 0.005.
Cerman et al. 2016[17]	Case-control	49 Pso × 47 controls	NLR significantly higher in psoriasis (2.62 ± 1.46 vs 1.60 ± 0.56; p < 0.001); No correlation with disease severity (p > 0.05).	NLR with possible prognostic value for cardiovascular diseases, relevant to check in psoriasis.
Asashina et al. 2017[21]	Case-control	186 Pso × 50 PsA	NLR significantly higher in PsA compared with Pso (3.53 ± 1.84 vs 2.71 ± 1.66; p < 0.001).	Mean NLR decreased significantly after 12 months of biological therapy; possible simple, convenient and cost-effective biomarker to monitor disease course after therapy.
Karabay et al. 2019[15]	Case-control	94 Pso × 118 controls	Higher mean NLR in psoriasis compared to controls [1.96 (1.65–2.34) vs 1.77 (1.31–2.43); p = 0.038] and higher in moderate to severe psoriasis (PASI < 10: 1.94 (1.59–2.18) vs PASI ≥ 10: 2.02 (1.69–2.86); p = 0.024.	Relation between disease and inflammatory parameters. NLR as possible for early detection of cardiovascular comorbidities.
Hammad et al. 2020[20]	Case-control	36 Pso 36 controls	NLR significantly higher than controls (2.48 ± 1.78 vs 1.24 ± 0.30; p < 0.001). NLR positively correlated with disease duration (r = 0.414; p = 0.012). No significant correlation between NLR and PASI (r = 0.265; p = 0.118).	NLR as a biomarker for systemic inflammation in Pso. Increased NLR influenced by disease duration, not severity.

By analyzing neutrophil-lymphocyte levels and mean platelet volume in psoriasis patients to investigate the relationship between these biomarkers and disease activity, Çerman et al.[18] found that NLR levels were significantly higher in psoriasis patients when compared to the control group.

These authors have come to the conclusion that NLR can be a good alternative in the global assessment of the patient, in evaluating psoriatic disease, in addition to monitoring the remission of skin lesions, since it is easy to access, available and inexpensive. In that regard, with a focus on comorbidities, the assessment of the inflammatory status using NLR could have an impact on cardiovascular comorbidities, which are not rarely associated with psoriatic disease. It is known that psoriasis itself is a major risk factor for cardiovascular and cerebrovascular events. Therefore, besides the intervention in modifiable risk factors, greater attention could be given to patients with higher NLR.

On the other hand, Ataseven et al.[17], despite demonstrating higher mean NLR among sick patients, found no correlation between Psoriasis severity scores (PASI) and NLR. Along these lines, when investigating the association between NLR and clinical severity of psoriasis, through a systematic review of literature, Paliogiannis et al.[19] found that there were no significant differences in NLR values according to disease severity. The authors concluded that NLR could be significantly associated with the presence of psoriasis but not its severity. Hammad et al.[20] suggest that NLR could be more related to the duration of the disease than to its severity.

Neutrophil-lymphocyte ratio (NLR) has been proposed as a possible marker for diagnosing and even predicting the risk of joint disease. Asahina et al.[21], in a case-control study, observed a higher NLR, as well as increased highly sensitive C-reactive protein, among patients with psoriatic arthritis when compared to patients with psoriasis without established joint involvement. Another interesting aspect of the same study was the perception of the normalization of NLR after treatment with immunobiological, suggesting that it can serve as a follow-up tool. Similarly, Kim et al.[16] observed a higher NLR in psoriatic arthritis when compared to patients with only psoriasis vulgaris and with healthy subjects, considering it a strong predictor of joint disease [odds ratio (OR) 3351, p = 0.005]. The present study found no difference in NLR levels between patients with (2.08) and without psoriatic arthritis (1.94/p = 0.957).

A compilation of the studies included in this review is presented in Table 5.

As stated, there is no contradiction that NLR, an emerging biochemical marker of inflammation, is higher in patients with psoriasis compared to the control group. Therefore, it can be used to assess the inflammatory status of psoriasis and serve even in the follow-up of treatment. On the other hand, further studies are needed to determine the additional usefulness of NLR in psoriasis disease.

Conclusion

Neutrophil-lymphocyte ratio (NLR) was higher in patients with psoriasis compared to the control group. NLR is an emerging inflammatory biomarker that is simple, accessible at all levels of healthcare, and easily calculated as part of the routine care of patients with psoriasis, and it can be used to evaluate inflammation and contribute to the management of psoriatic patients. However, further studies are needed to determine the real value and other applications for NLR in psoriatic disease.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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ORIGINAL ARTICLE

The impact of COVID-19 pandemics on malignant melanoma: the experience of a single center

O impacto da pandemia COVID-19 no melanoma maligno: a experiência de um centro

Maria J. Guimarães[1,a], Carlos M. Nogueira[1], Catarina Cerqueira[1], Ana G. Lopes[1], Ana P. Vieira[1], Cristiana Macedo[1], Teresa Pereira[1], Joana Gomes[1], Catarina Araújo[1], Sofia Lopes[1], André Coelho[2], Joana Pardal[3], Fernando Pardal[3], and Celeste Brito[1]*

[1]Service of Dermatology and Venereology, Hospital de Braga; [2]Department of Pathological Anatomy, Unilabs; [3]Pathological Anatomy Department, Hospital de Braga, Braga, Portugal
[a]ORCID: 0000-0002-3247-2470

Abstract

Introduction: The pandemic outbreak of coronavirus disease 2019 (COVID-19) greatly restricted routine healthcare services across Europe, including cancer diagnosis and treatment. Amongst skin cancers, malignant melanoma (MM) is responsible for most deaths. **Objective:** This study aimed to compare the number and characteristics of diagnosed MM cases before and during the pandemic in a Portuguese secondary hospital. **Methods:** This was an observational, retrospective study comparing a prepandemic (diagnosis from March 2019 to February 2020) and a pandemic group of patients with MM diagnosis (diagnosis between March 2020 and February 2021). **Results:** A total of 59 patients were included, 44 in the pre-pandemic group and 15 in the pandemic period. In the first year of the pandemic, there was a significantly lower number of MM diagnoses compared to the precedent year (15 vs 44, $p < 0.01$), without significant differences in tumor characteristics. The time from referral to first consultation was slightly shorter in the pandemic group (median of 36 vs 76 days, $p = 0.056$). **Conclusions:** This study provides evidence of a reduction in MM diagnosis during the first year of the COVID pandemic, despite no significant differences in prognostic factors. As the pandemic persists, one must emphasize the importance of early MM diagnosis and treatment.

Keywords: Skin cancer. Severe acute respiratory syndrome coronavirus 2. Malignant melanoma. Coronavirus disease of 2019.

Resumo

Introdução: A pandemia Coronavírus 2019 restringiu consideravelmente os serviços de saúde de rotina em toda a Europa, incluindo o diagnóstico e tratamento de cancro. De entre os cancros da pele, o melanoma maligno (MM) é o responsável pela maioria das mortes. **Objetivo:** Este estudo teve como objetivo comparar o número e características dos MM diagnosticados antes e durante a pandemia num hospital secundário português. **Métodos:** Estudo observacional, retrospectivo, que comparou o grupo de doentes pré-pandémico (diagnóstico de MM de março de 2019 a fevereiro de 2020) e pandémico (diagnóstico de MM entre março de 2020 e fevereiro de 2021). **Resultados:** Foram incluídos 59 doentes, 44 do grupo pré-pandémico e 15 no período pandémico. No primeiro ano da pandemia, houve uma redução significativa dos diagnósticos

***Corresponding author:**
Maria J. Guimarães
E-mail: mjcunhaguimaraes@gmail.com

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de melanoma maligno relativamente ao ano anterior (15 vs. 44, p < 0,01), sem diferenças significativas nas características dos tumores. **Conclusões:** Este estudo mostra uma redução dos diagnósticos de MM durante o primeiro ano da pandemia, embora sem diferenças significativas nos fatores de prognóstico. Com a persistência da pandemia, deve-se enfatizar a importância do diagnóstico e tratamento precoce do MM.

Palavras-chave: Cancro da pele. SARS-CoV-2. Melanoma maligno. COVID-19.

Introduction

The pandemic outbreak of COVID-19 greatly restricted routine healthcare services across Europe, including cancer diagnosis and treatment[1-3]. The first COVID-19 case in Portugal was confirmed on 2nd March 2020. The country entered a lockdown (state of emergency) two weeks later, which began to be lifted on 2nd May 2020[3].

Most healthcare settings implemented minimal services, which, along with the fear of the population getting infected with COVID-19, led to the cancelation or suspension of programmed activity[4,5]. Globally, the World Health Organization estimated that 40% of countries reported partial or complete disruptions in cancer treatment[6].

Therefore, it is essential to assess whether healthcare limitations led to a reduction in the diagnosis and delays in the treatment of skin cancer, particularly MM since it is responsible for most skin cancer deaths[2,5].

The outcome of MM depends primarily on tumor thickness, which, in turn, is related to the time to diagnosis[2]. Thin MMs are preferentially diagnosed through screening by experienced dermatologists, whereas patient-identified MMs are tendentially thicker and diagnosed at advanced stages[7].

A model based on melanoma rate of growth built by Tejera-Vaquerizo estimated that a 3-month diagnosis delay in melanoma would represent an upstaging of 45% of cases and a 2% loss in 5-year survival[8].

There are already studies across Europe documenting the impact of the pandemic on MM diagnosis and prognosis in several countries[4]. Most of them report a reduction in the number of MM diagnoses in the pandemic era, along with a higher Breslow depth index and TNM staging[4]. One single similar Portuguese study was conducted in IPO Porto, one of the largest cancer-dedicated hospitals in Portugal[3]. The authors compared the impact of the COVID-19 outbreak on the short-term survival of several types of cancer, comparing a period of 4 months after the beginning of the outbreak in Portugal (2nd March 2020) with the same period in the previous year[3]. A reduction of 30% of patients diagnosed with melanoma was noted after the pandemic onset, however, without impact on short-term survival[3]. However, this study doesn't particularize the characteristics of melanoma diagnoses before and during the pandemic, which would be important to assess prognosis and impact beyond short-term survival[3].

This study aims to compare the number of diagnosed MM before and during the pandemic in a Portuguese secondary hospital and determine if there were differences in tumor characteristics, namely Breslow depth index, mitotic rate, ulceration, and tumor stage.

Methods

This was an observational, single-center, retrospective study, including patients diagnosed with cutaneous MM between March 2019 and February 2021 at the Dermatology Department of Hospital de Braga, Portugal.

The demographical clinical and anatomopathological data were collected from clinical files. Patients without histopathological confirmation of MM were excluded from the analysis.

A comparative analysis of two groups: pre-pandemic (MM diagnosis from March 2019 to February 2020) and pandemic (diagnosis of MM from March 2020 to February 2021), was performed.

The patient's identity was not disclosed in this research. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The collected data were analyzed using the statistical software for Windows, Statistical Package for the Social Sciences v27 (IBM Corp., Armonk, New York, United States of America). Categorical variables were described by frequency and proportion; summary statistics (median, range) were used to report continuous data. Differences between the two groups were tested by Mann-Whitney *U* test (for continuous variables) and by the Chi-squared test (for categorical variables), as appropriate. A two-sided p-value of < 0.05 was considered statistically significant.

Table 1. Characterization of patients and tumors

		Pre-pandemic n (%)	Pandemic n (%)	p-value
Number of diagnoses		44 (74.6%)	15 (25.4%)	**< 0.01***
Age (years; median)		72	67	0.565
Sex	Male	16 (36.4%)	6 (40%)	0.801
	Female	28 (64.6%)	9 (60%)	
MM localization	Head	23 (52.3%)	4 (26.7%)	0.286
	Trunk	7 (15.9%)	4 (26.7%)	
	Upper limb	7 (15.9%)	2 (13.3%)	
	Lower limb	7 (15.9%)	5 (33.3%)	
MM	In situ	18 (40.9%)	5 (33.3%)	0.603
	Invasive	26 (59.1%)	10 (66.7%)	
MM subtype	LM	15 (34.1%)	4 (26.7%)	0.469
	MM acral in situ	1 (2.3%)	0 (0%)	
	MM in situ	2 (4.6%)	1 (6.7%)	
	LMM	2 (4.6%)	1 (6.7%)	
	MM acral	0 (0%)	1 (6,7%)	
	SSMM	17 (38.6%)	8 (53.3%)	
	Nodular MM	6 (13.6%)	0 (0%)	
	MM NOS	1 (2.3%)	0 (0%)	
Breslow thickness (mm; median)		1.08	1.2	0.806
Ulceration[a]	Yes	8 (18.2%)	0 (0%)	0.089
	No	18 (10.9%)	10 (66.7%)	
Number of mitosis (median)		2.5	1	0.213
Stage	0	18 (40.9%)	5 (33.3%)	0.469
	IA	9 (20.5%)	3 (20%)	
	IB	5 (11.4%)	4 (26.7%)	
	IIA	1 (2.3%)	2 (13.3%)	
	IIB	4 (9.1%)	1 (6.7%)	
	IIC	5 (11.4%)	0 (0%)	
	NOS	2 (4.6%)	0 (0%)	
Referral source	Family doctor	33 (75%)	12 (80%)	0.322
	Dermatology dept	3 (6.8%)	3 (20%)	
	Emergency dept	4 (9.1%)	0 (0%)	
	Other speciality	1 (2.3%)	0 (0%)	
	External	3 (6.8%)	0 (0%)	
Time to first dermatology appointment (days; median)		73	36	0.059
Time to surgery (days; median)		23	13	0.393

MM: malignant melanoma; LM: lentigo maligna; LMM: lentigo maligna melanoma; SSMM: superficial spreading malignant melanoma; NOS: not otherwise specified; dept: department; p bold*: statistically significant (< 0.05) calculated by Chi-squared test; [a]: in the invasive melanomas.

Results

A total of 59 patients were included, 44 in the prepandemic group and 15 in the pandemic period. The characteristics of patients and tumors are described in Table 1.

In the 1st year of the pandemic, there was a significantly lower number of MM diagnoses compared to the

precedent year (15 vs 44, p < 0.01), which corresponds to a decrease of 65.9% in the number of diagnoses. Notably, there were no diagnoses in March, April, and May 2020 (the first lockdown period).

There were no statistically significant differences in ages between groups, with a median age of 72 and 67 years of the pre-pandemic and pandemic groups, respectively. Most of the patients were women in both groups (64.6 and 60% in the prepandemic and pandemic groups, respectively), without differences in sex distribution.

The most common tumor location was the head in the pre-pandemic group (52.3% of tumors), while in the pandemic group, it was the lower limb (33.3%), although this difference did not reach statistical significance.

Regarding the proportion of *in situ* vs invasive MM, there were no differences between groups, though, in the pandemic group, we found an increase in invasive MM (66.7 vs 59.1%). There were also no differences concerning the MM subtype or staging, with a greater proportion of superficial spreading MM in both groups, consistent with a predominance of lower stages (0 and I).

Breslow depth index was slightly higher in the pandemic group (median 1.2 vs 1.08 mm). However, this difference did not reach statistical significance. We also found no differences in what concerns ulceration or mitotic index.

Regarding the referral source, the family doctor was preponderant in both groups, without significant differences between them. The time from referral to first consultation was marginally significantly shorter in the pandemic group (median of 36 vs 76 days, p = 0.056), and there was no significant difference among groups in the time from first dermatology appointment to surgery.

Discussion

The main finding of this study is a significant reduction in the number of MM diagnoses in the first year of pandemics (a decrease of 65.9% of diagnoses, p < 0.01). Similarly, other studies also reported a reduction of MM diagnosis, although with a lower expression[4,7,9-11]. Some of these studies report a more pronounced reduction in *in situ* and thin MM, translating into a higher proportion of invasive MM[4,7,11]. In our study, we observed a slight increase in invasive MM in the pandemic group, although without statistical significance. Since we found a major reduction in the number of MM diagnoses, the reduced sample in the pandemic group may explain the lack of statistical significance; however, we believe that these results are worth mentioning.

Regarding prognostic factors, such as the Breslow depth index, ulceration, or mitotic index, there were no differences between groups, which translates into a similar staging distribution. In contrast, other authors found higher Breslow depths and mitotic rates and, consequently, a shift toward more advanced stages in pandemic groups[4,7,10,11].

Surprisingly, we found a marginally significant reduction in the time from referral to the first dermatology appointment in the pandemic group. This could be explained by the reduction of referrals of less urgent situations from primary care in this period and the maintenance of the outpatient activity of the Dermatology Department. Similarly, Andrew and associates also found a decrease in skin cancer diagnoses accompanied by a reduction in waiting time for the first appointment during the first 3 months of COVID-19[12].

In what concerns to the referral source, primary care remained preponderant in both periods, reinforcing the role of the family doctor in the detection of suspected lesions.

The main limitation of this study is the inclusion of one single center with a small sample. This might have impacted the obtention of statistically significant results. Including more centers and cancer referral centers would overcome this limitation and would allow us to see the "bigger picture" and better understand the real impact of the pandemics on MM in Portugal. However, the authors still consider this a relevant study since it is the first of this kind to include Portuguese data. Furthermore, cause-effect relationships are difficult to assess from retrospective observational data, and the impact of confounding factors is unknown. Moreover, we believe the reduction of melanoma diagnoses in the COVID era may reflect a higher threshold in seeking medical care due to fear of infection by the general public rather than a true reduction in melanoma incidence.

Conclusion

In conclusion, this study provides evidence of a reduction in MM diagnosis during the first year of the pandemic in a Portuguese center. Reasons for this would require further analysis. It can be speculated that this could happen due to limitations on access to Primary care, which is the main referral source of MM patients, and the fear of COVID-19 from the population, avoiding medical consultations. As the pandemic persists, it is essential to reinforce among the population and health professionals the importance of screening and prompt treatment of melanoma.

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Conflicts of interest

None.

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. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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REVIEW ARTICLE

Alopecia areata: from pathophysiology to therapeutic innovation

Alopecia areata: da fisiopatologia à inovação terapêutica

*Nuno Lourenço[1] and Margarida Gonçalo[1,2,a]**

[1]Faculty of Medicine, Universidade de Coimbra; [2]Dermatology Service, Clínica Universitária de Dermatologia, Hospitalar e Universitário de Coimbra, Coimbra, Portugal

[a]ORCID: 0000-0001-6842-1360

Abstract

Alopecia areata (AA) is a chronic disease characterized by non-scarring hair loss, ranging from patches on the scalp to total body hair loss. The major event in the pathophysiology of AA is the breakdown of the immune privilege of the hair follicle caused by increased local production of interferon-gamma (IFN-γ). As a result, in the majority of the cases, there is autoantigen recognition with infiltration of autoreactive T cells, and a series of inflammatory changes in the hair follicle microenvironment, largely mediated by the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Based on these pathophysiological findings, the JAK-STAT pathway has been defined as a therapeutic target in AA, with JAK inhibitors emerging as an alternative to traditional nonspecific treatments. Initially, first-generation oral JAK inhibitors (baricitinib, tofacitinib, and ruxolitinib) and, more recently, second-generation oral JAK inhibitors (ritlecitinib, brepocitinib, upadacitinib, and abrocitinib) have demonstrated efficacy and safety in the treatment of AA. Following positive results from the BRAVE-AA1 and BRAVE-AA2 studies, oral baricitinib (Olumiant) became the first drug ever approved for the treatment of AA on 13th June 2022. In contrast, topical JAK inhibitors, as well as other novel therapies such as phosphodiesterase-4 inhibitors (apremilast) and biologics (dupilumab, secukinumab, and aldesleukin), appear to have limited efficacy in the treatment of AA, with the possible exception of dupilumab. Thus, the aim of this article is to review the pathophysiological mechanisms and new targeted treatments in AA, with a special focus on JAK inhibitors.

Keywords: Alopecia areata. Pathophysiology. JAK inhibitors. Baricitinib. Phosphodiesterase-4 inhibitors. Biologics.

Resumo

A Alopecia areata (AA) é uma doença autoimune crónica caracterizada pela perda de cabelo não-cicatricial, que varia desde peladas à perda de todos os pelos do corpo. O evento major na fisiopatologia da AA é o colapso do privilégio imunológico do folículo piloso causado pelo aumento da produção local de interferão-gama (IFN-γ). Como consequência, na maioria dos casos, há um reconhecimento dos autoantigénios por um infiltrado imune de linfócitos T autorreativos e um conjunto de alterações inflamatórias no microambiente do folículo piloso, em grande parte mediadas pela via Janus cinase–transdutor de sinal e ativador da transcrição (JAK-STAT). Com base nestes achados fisiopatológicos, a via JAK-STAT foi definida como alvo terapêutico na AA, com o desenvolvimento dos inibidores JAK, que surgem como alternativa aos tratamentos tradicionais inespecíficos. Inicialmente, os inibidores JAK de 1ª geração orais (baricitinib, tofacitinib e ruxolitinib) e, mais recentemente,

***Corresponding author:**
Margarida Gonçalo
E-mail: mgoncalofmed.uc.pt

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os inibidores JAK de 2ª geração orais (ritlecitinib, brepocitinib, upadacitinib e abrocitinib) têm demonstrado eficácia e segurança no tratamento da AA. No seguimento de resultados positivos nos estudos BRAVE-AA1 e BRAVE-AA2, o baricitinib oral (Olumiant) foi o primeiro fármaco de sempre a receber aprovação para o tratamento da AA, no dia 13 de Junho de 2022. Pelo contrário, os inibidores JAK tópicos e outras terapêuticas inovadores, tais como os inibidores da fosfodiesterase-4 (apremilast) e os biológicos (dupilumab, secukinumab e aldesleukin), parecem ter uma eficácia limitada no tratamento da AA, com a possível exceção do dupilumab. Desta forma, o presente artigo propõe-se a rever os mecanismos fisiopatológicos e novos tratamentos dirigidos na AA, com especial foco nos inibidores JAK.

Palavras-chave: Alopecia areata. Fisiopatologia. Inibidores JAK. Baricitinib. Inibidores da fosfodiesterase-4. Biológicos.

Introduction

Alopecia areata (AA) is a chronic autoimmune disease characterized by reversible, non-scarring hair loss. The most common pattern consists of hair loss in circumscribed, irregular patches of the scalp, which may progress to total scalp hair loss [alopecia totalis (AT)] or complete body hair loss [alopecia universalis (AU)]. Other less common forms of presentation include ophiasis AA, diffuse AA, and AA reticularis[1,2].

Alopecia areata (AA) is the second most common cause of hair loss after androgenetic alopecia, affecting approximately 2% of the world's population over the course of a lifetime. The prevalence is higher in children and adolescents, with both sexes being equally affected[3]. There is also a higher prevalence of AA in people with other autoimmune diseases such as vitiligo, atopic dermatitis, psoriasis, and thyroid disease[4]. The diagnosis of AA is clinical, but trichoscopy or, seldom, a skin biopsy may be necessary[5].

Alopecia areata (AA) is a chronic and unpredictable disease in which patients experience periods of remission alternating with relapses. As a result, the quality of life is greatly affected, and AA is associated with a higher risk of psychological disorders such as depression and anxiety[3].

Alopecia areata (AA) is considered a multifactorial disease involving complex interactions between genetic, environmental, and immunologic factors[6]. The pathophysiology of AA was largely unknown until recently, but several advances have been made in this area, particularly in relation to immune factors. Recent studies suggest that the loss of the immune privilege of the hair follicle is at the origin of AA. There is an activation of cluster of differentiayion (CD8+) T cells *via* the JAK-STAT pathway, and these cytotoxic T cells attack the hair follicle and disrupt its normal growth cycle[1,2,6].

Currently, there is no curative treatment for AA. Traditional treatments are used off-label and have variable and transient efficacy, often with significant adverse effects[4]. According to international guidelines, the management of AA includes mostly topical, systemic and intralesional corticosteroids, and contact immunotherapy. The individual therapeutic approach depends mainly on age, severity, and stage of the disease (acute or chronic)[5,7].

In most cases, topical and/or intralesional corticosteroids are the first line of treatment, especially in more localized forms of AA[3,6,8]. In refractory cases or in acute forms of severe AA, oral corticosteroids or, less frequently, intravenous corticosteroid pulse therapy may be used[3,5]. Prolonged use of these systemic corticosteroids is associated with multiple adverse effects, including weight gain, osteoporosis, and glucose intolerance, and therefore should only be used for short periods[3,6]. Contact immunotherapy with diphenylcyclopropenone or squaric acid dibutyl ester is mostly used as a second-line treatment in patients with chronic severe AA[3,5,8]. Additionally, topical anthralin is an alternative to corticosteroids in pediatric patients with severe AA[3].

All these treatments are symptom-oriented and use their immunosuppressive and immunomodulatory properties unspecifically, which justifies their limited efficacy and safety[3]. However, the discovery of the importance of the JAK-STAT pathway in the pathophysiology of AA has led to the emergence of new, more targeted therapeutic options: JAK inhibitors. In recent years, several studies with JAK inhibitors have been conducted and have shown promising results in terms of efficacy and safety. Other innovative treatments, also targeting pathophysiological mechanisms, include apremilast, a phosphodiesterase-4 inhibitor, and biological therapies, such as dupilumab[9].

Thus, given these recent advances, our aim is to review the scientific evidence regarding the pathophysiology of AA and data on the efficacy and safety of the new treatments for AA.

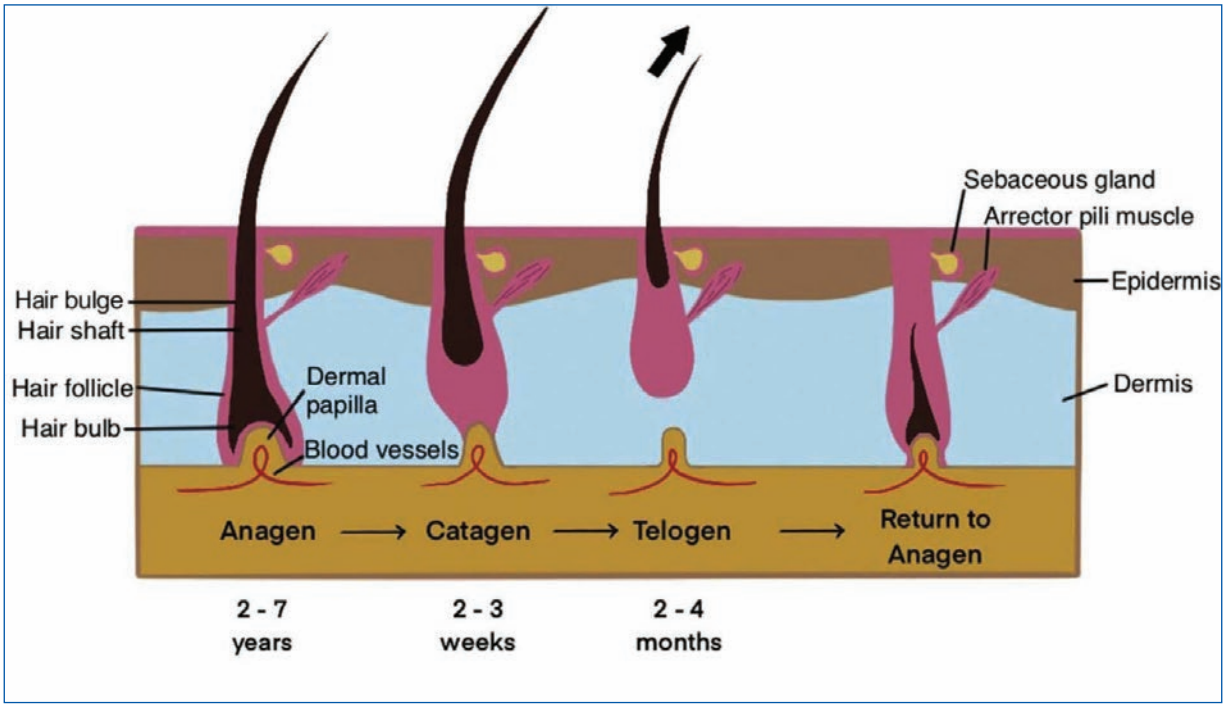

Figure 1. Hair growth cycle. *Adapted from Olayinka et al.*[2].

Pathophysiology

Disruption of the hair growth cycle

Alopecia areata (AA) is a disease that affects the hair follicle, a unique mini-organ that undergoes a cyclic and regenerative process throughout life[3,10,11]. The normal hair cycle is divided into three major phases-anagen (growth), catagen (involution), and telogen (rest)[2,6,11-14]. Some authors also consider a fourth phase, exogen, of hair shedding and return to anagen[2,14].

Anagen is the longest phase of the hair cycle (lasting between 2 and 7 years) and is the phase in which most scalp hair (between 88 and 90%) is found at any given time in a person's life. During this phase, the hair follicle actively receives nourishment from the blood vessels in the dermal papilla, leading to differentiation and proliferation of epithelial cells in the proximal direction, with hair growth. During catagen, the hair follicle begins to separate from the dermal papilla due to epithelial cell apoptosis. This is a transient process, lasting 2-3 weeks, and is followed by telogen, which lasts 2-4 months. At this phase, the hair follicle enters a period of relative quiescence and separates completely from the dermal papilla and, thereafter, from its only source of nutrients, culminating in hair loss (exogen phase). Then, there is a return to anagen, and a new hair cycle begins, which is repeated throughout life (Fig. 1)[2,11,12]. Keratinocyte and melanocyte stem cells, mainly located in the bulge area of the hair follicle, makes this cyclic process possible[11].

However, in AA patients, there is a disruption in the normal hair growth cycle, with shortened anagen time and premature entry into the more advanced stages of catagen[3,6,11,12,15] and telogen[2,6,12-14], which is clinically manifested by hair loss.

Genetic susceptibility and environmental triggers

The exact cause of AA is unknown, but it is believed to have a multifactorial background, resulting from a combination of environmental influences and genetic factors involved in the immune system response[10].

In fact, hundreds of single nucleotide polymorphisms have already been identified in AA patients, many of them in genes related to activation and proliferation of regulatory and CD8+ T cells, interleukin (IL) expression, and autoantigen presentation. Among them, it is important to highlight the human leukocyte antigen genomic region on chromosome 6, which encodes the major histocompatibility complex (MHC), as a major contributor to the AA phenotype[16]. Additionally, other

genes located on the same chromosome, encoding the natural killer group 2D (NKG2D+) receptor and its danger ligands, have been shown to play an important role in the pathophysiology of AA, as discussed below[13,16].

It is believed that in these genetically susceptible individuals, environmental triggers, such as physical or psychological stress, viral infections, or hair follicle microtrauma, can contribute to the dysregulation of immune mechanisms and the development of AA[3]. However, in most cases, no obvious trigger for the disease onset is found[13].

Collapse of the immune privilege

In the hair follicle, there are immune-privileged areas, similar to other body regions such as the central nervous system, testicles, placenta, and eyes. The hair bulge during the entire hair cycle and the hair bulb only during the anagen phase is such immune-privileged areas, where antigens, although recognized by the immune system, do not generate an immune-inflammatory response[17]. This concept of immune privilege is essential for maintaining homeostasis and normal hair growth[4].

Several mechanisms are responsible for maintaining immune privilege in the hair follicle–downregulation of MHC class I expression, which prevents the presentation of autoantigens to CD8+ T cells; production of potent immunosuppressants, such as transforming growth factor beta-1 (TGF β-1), IL-10, and insulin-like growth factor-1; increased expression of Fas ligand and programmed death ligand 1, pro-apoptotic molecules that target autoreactive T cells; and physical barriers, such as the absence of lymphatic drainage and the presence of a proteoglycan-rich, thick extracellular matrix that blocks the passage of immune cells[4,6,17].

Dysregulation of these immune-tolerance mechanisms, caused by a local increase in IFN-γ, leads to the collapse of the hair follicle immune privilege, which is considered the major event in the pathophysiology of AA[5,13,18,19]. As a result, there is increased exposure of anagen hair follicle autoantigens to autoreactive CD8+ T cells that attack the hair follicle in the anagen phase, causing a premature transition to the catagen and telogen phases[6,19]. During the active phases of the disease, the immune attack is concentrated mainly in the bulb region, sparing the stem cells in the bulge area. This phenomenon explains the reversibility of hair loss in AA[3,15].

More recently, Bertolini et al. have shown that not all AA is truly autoimmune and that a classic autoimmune cascade occurs only in a subset of AA patients[19]. In these cases, ectopic expression of melanogenesis-associated antigens recognized by CD8+ T cells leads to a local increase in IFN-γ signaling ["autoimmune, AA"]. In other patients, the pro-inflammatory activity of innate immune cells (NK cells, mast cells) induces IFN-γ production in a non-autoantigen-specific manner ("non-autoimmune"). Ultimately, both forms of AA coalesce in the collapse of hair follicle immune privilege, followed by increased antigen exposure and an influx of autoreactive immune cells. Thus, AA may represent a stereotypic response pattern to IFN-γ-induced hair follicle damage[19,20].

In fact, there are profound changes in the hair follicle microenvironment in AA, with upregulation of danger ligands (activators of CD8+ T cells), presence of a robust immune infiltrate, increased levels of several pro-inflammatory cytokines, and increased expression of MHC class I and MHC class II[10].

Overexpression of danger ligands, which activate a subpopulation of CD8+ T cells that express NKG2D+ receptors, is suggested as one of the mechanisms involved in the loss of immune privilege. These ligands include UL-16 binding protein-3 and MHC class I polypeptide-related sequence A. Recent studies have shown that hair follicles of AA patients have elevated levels of these two danger ligands compared to "healthy" hair follicles[18,21].

In addition, there is a strong presence of an inflammatory infiltrate in the lesional hair follicles, composed mainly of CD8+ and CD4+ T cells, as well as Natural Killer (NK) cells, mast cells, and dendritic cells, which are described histologically as a “swarm of bees”. Among these immune cells, CD8+ NKG2D+ T cells stand out as the main effectors in AA and the first to infiltrate hair follicles[3,19,21]. These CD8+ NKG2D+ T cells have been shown to be necessary and sufficient to induce AA in murine models of the disease in a study conducted by Xing et al.[37] Activated CD8+ T cells, in addition to their cytotoxic action through granzyme B, produce potent pro-inflammatory cytokines, such as IFN-γ and tumor necrosis factor-alpha (TNF-α), which prolong the immune-inflammatory state around and within the hair follicle[10,16].

Local production of IFN-γ is considered the main mechanism responsible for the collapse of the hair follicle immune privilege[5,19]. This cytokine induces MHC class I and class II expression along the lower follicular epithelium, enhancing the presentation of autoantigens, respectively, to CD8+ and CD4+ T cells[22]. Moreover, IFN-γ induces the expression of CXC motif chemokines

ligands 9 and 10, which attract and recruit circulating T cells, perpetuating the inflammatory state of the hair follicle[17,22]. There are other pro-inflammatory cytokines, such as IL-7 and IL-15, which are increased in AA and are essential for the survival of CD8+ NKG2D+ T cells and stimulation of their cytotoxic activity[14,22].

Thus, AA is clearly associated with a type 1 immune response, with the involvement of IFN-γ as the main inflammatory mediator and activation of CD8+ and CD4+ T helper 1 (Th1) cells[5,22,23]. Th1 cells actively participate in the immune response by producing type 1 cytokines, such as IL-2, IL-12, IFN-γ, and TNF-γ [23]. Recent studies further suggest the involvement of Th2 (type 2 immune response) and Th17 cells in the pathophysiology of AA, as high levels of Th2 cytokines, such as IL-4 and IL-13, and Th17 cytokines, such as IL-17 and IL-21, have been detected in the serum of AA patients[5,23]. However, the exact role of these pro-inflammatory cytokines in AA is not so well understood, and more studies are needed to clarify it.

As in other autoimmune diseases, AA is associated with an impairment of cellular regulatory mechanisms, dysfunction and a decrease in the number of regulatory T cells, as demonstrated in a human study[24].

Role of the JAK-STAT pathway

Many of these immunoinflammatory responses implicated in the pathophysiology of AA share a common intracellular signaling pathway–the JAK-STAT pathway[3,4].

Janus kinase-signal transducer and activator of transcription (JAK-STAT) is an intracellular signaling pathway consisting of the receptor, Janus kinase (JAK), and signal transducer and activator of transcription (STAT). The JAK family consists of three JAKs (JAK 1-3) and a tyrosine kinase 2 (TYK2), while the STAT family contains seven STATs (STAT1-4, STAT5A, STAT5B, and STAT6). Depending on the ligand and receptor, different combinations of JAKs and STATs are activated[3]. When a specific ligand binds to the receptor in the cell membrane, the JAK protein phosphorylates its tyrosine component, activating its kinase function, which, in turn, phosphorylates the STAT component. This leads to the dimerization and activation of STAT, which translocates into the cell nucleus and acts as a regulator of the transcription of specific regions of DNA, modulating gene expression[18].

In AA, the JAK-STAT pathway promotes the production of pro-inflammatory cytokines, such as IFN-γ and IL-15, with the participation of CD8+ NKG2D+ T cells and follicular epithelial cells. Indeed, CD8+ NKG2D+ T cells, activated by autoantigens, produce IFN-γ, which binds to its receptors on follicular epithelial cells and promotes the production of IL-15 through JAK-1 and JAK-2. In turn, IL-15, in combination with IL-15 receptor-α, binds to its receptors on CD8+ NKG2D+ T cells and leads to IFN-γ production via JAK-1 and JAK-3, completing the positive feedback loop that amplifies the local inflammatory response (Fig. 2)[3,15,25].

These findings have led to the development of drugs such as baricitinib, tofacitinib, and ruxolitinib (Fig. 2), which are JAK inhibitors and, therefore, potential treatments targeting AA, as discussed next[25].

New treatments

Janus kinase (JAK) inhibitors

Janus kinase (JAK) inhibitors belong to a class of immunomodulatory drugs that have been widely studied over the years in the treatment of various inflammatory diseases, such as psoriasis, rheumatoid arthritis, and myelodysplastic diseases, and have recently attracted the attention of dermatologists for the treatment of AA[6,9].

Janus kinase (JAK) inhibitors work by preventing the binding of adenosine triphosphate to the kinase domain of the JAK enzyme, an essential event for the phosphorylation of tyrosine residues. As a result, there is no tyrosine phosphorylation, and subsequent events in the JAK-STAT pathway are inhibited[10]. The researchers began to focus on JAK enzymes rather than other "players" involved in the pathophysiology of AA when it became clear that blocking cytokines such as IFN-γ or IL-15 was not sufficient to reverse AA, and the STATs could not be a good pharmacological target because they lacked catalytic activity[26].

Janus kinase (JAK) inhibitors are divided into two groups–1st generation, the first to be developed, and 2nd generation, more recently developed. First-generation JAK inhibitors are less selective, showing activity against multiple JAK enzymes, while second-generation JAK inhibitors are more selective, inhibiting only one or two specific JAK enzymes[6].

Before discussing JAK inhibitors in more detail, it is important to highlight a score created by Olsen et al. to standardize the assessment of AA severity in clinical trials–the severity of alopecia tool (SALT) score[27]. It is a simple and reproducible score that divides the scalp into four quadrants, each represented by a percentage (%) of its total area–left side (18%), right side (18%), top (40%), and back (24%).

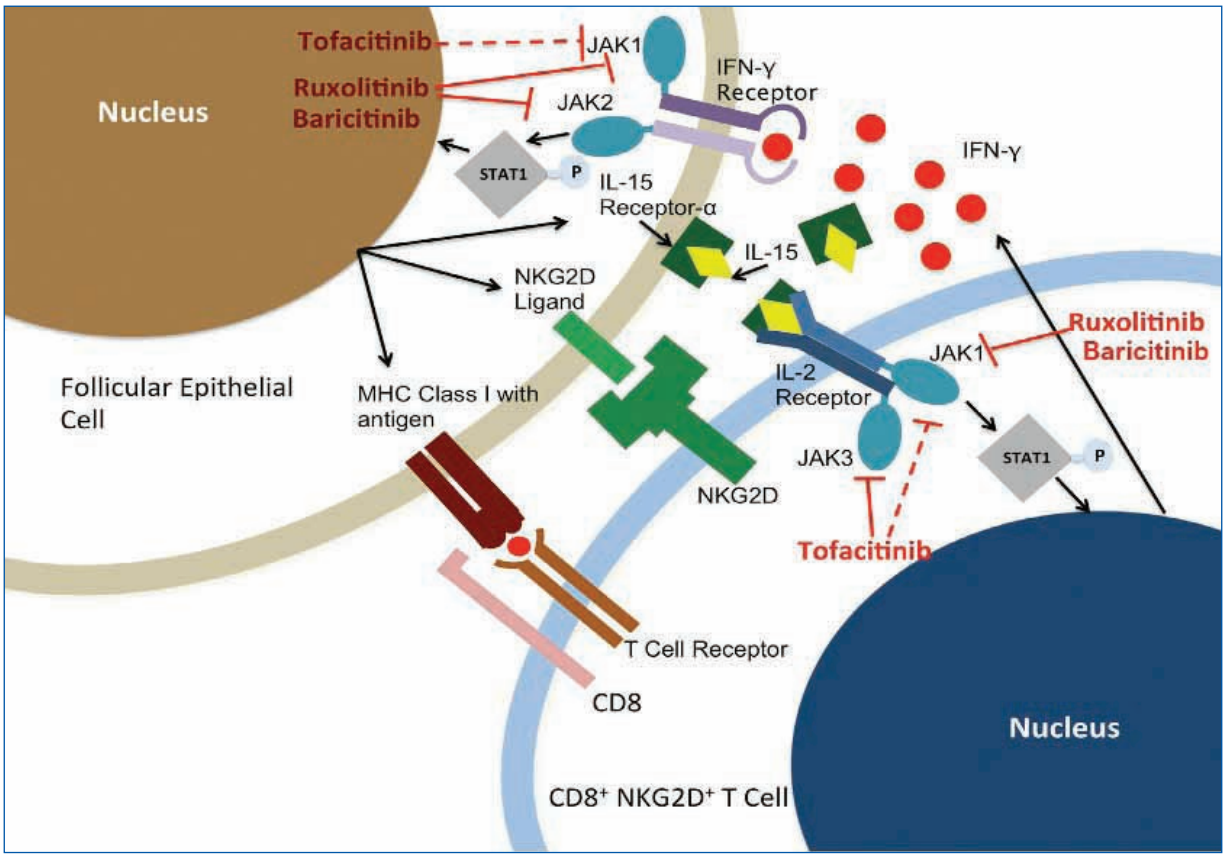

Figure 2. Interaction between CD8+ NKG2D+ T cells and follicular epithelial cells mediated by the JAK-STAT signaling pathway and the role of JAK inhibitors. *Adapted from Strazzulla et al.*[25]. Red bars represent the inhibitory capacity of JAK inhibitors. MHC: major histocompatibility complexes; NKG2D+: natural killer group 2D; IL: interleukin; JAK: Janus kinase; STAT: signal transducer and activator of transcription; IFN-γ: interferon-γ.

The percentage of hair loss in each quadrant is visually estimated and then summed to determine the SALT score–from 0 (no hair loss) to 100% (loss of all hair)[27]. A SALT score of 50% or greater has been defined as severe AA[28]. Most of the clinical trials we will review have hair growth as the primary outcome, using the post-treatment SALT score to make this assessment, or alternatively, the $SALT_n$ response, which compares the final SALT score to the baseline SALT score[27].

Oral baricitinib

Baricitinib is a first-generation JAK inhibitor that preferentially inhibits JAK1 and JAK2[22]. The efficacy of oral baricitinib in the treatment of AA was first suggested in 2015 in a case report of a patient with AA and chronic atypical neutrophilic dermatosis syndrome with lipodystrophy and elevated temperature who demonstrated complete hair regrowth after 9 months of treatment with baricitinib 11 mg/day[29].

More recently, large-scale clinical trials have been conducted to evaluate the efficacy and safety of oral baricitinib in the treatment of AA. The first study (BRAVE-AA1), a phase 2, double-blind, placebo-controlled, randomized clinical trial (RCT), enrolled 110 patients with severe AA (SALT score of ≥ 50%) into three groups-placebo, 2 and 4 mg of baricitinib once daily (1id)[30]. The primary endpoint was the proportion of patients with a SALT score of ≤ 20% (considered a clinically successful treatment of severe AA). After 36 weeks of treatment, the proportion of patients with a SALT score of ≤ 20% was significantly higher in the baricitinib 2 (33.3%) and 4 mg (51.9%) groups than in the placebo group (3.6%) (Table 1). Adverse events observed were mostly mild[30]. Next, the two phase 3, double-blind, placebo-controlled RCTs (BRAVE-AA1 and BRAVE-AA2) evaluating the efficacy and safety of 2 and 4 mg doses of oral baricitinib included 654 and 546 patients, respectively, divided into three groups: placebo, 2 and 4 mg of baricitinib 1id[31]. A similar primary outcome assessed at 36 weeks (SALT score of

Table 1. Summary of the main studies conducted with JAK inhibitors in the treatment of AA

JAK inhibitor	Study type	Nº of patients	Dosing	Primary outcome	Response (%)
Oral baricitinib[30,31]	Phase 2 RCT BRAVE-AA1	110	Baricitinib 4 mg, 1id	SALT ≤ 20% week 36	51.9%
			Baricitinib 2 mg, 1id		33.3%
			Placebo, 1id		3.6%
	Phase 3 RCT BRAVE-AA1	654	Baricitinib 4 mg, 1id	SALT ≤ 20% week 36	38.8%
			Baricitinib 2 mg, 1id		22.8%
			Placebo, 1id		6.2%
	Phase 3 RCT BRAVE-AA2	546	Baricitinib 4 mg, 1id	SALT ≤ 20% week 36	35.9%
			Baricitinib 2 mg, 1id		19.4%
			Placebo, 1id		3.3%
Oral tofacitinib[35]	Open-label clinical trial	66	Tofacitinib 5 mg, 2id	$SALT_{50}$ 3rd month	32%
Oral ruxolitinib and tofacitinib[38]	Open-label clinical trial	75	Ruxolitinib 20 mg, 2id	$SALT_{50}$ 6th month	84.2%
			Tofacitinib 5 mg, 2id		78.4%
Oral CTP-543[39,40]	Phase 2 RCT	149	CTP-543 12 mg, 2id	$SALT_{50}$ week 24	58%
			CTP-543 8 mg, 2id		47%
			CTP-543 4 mg, 2id		21%
			Placebo, 2id		9%
	Phase 3 RCT THRIVE-AA1	706	CTP-543 12 mg, 2id	SALT ≤ 20% week 24	41.5%
			CTP-543 8 mg, 2id		29.6%
			Placebo, 2id		0.8%
	Phase 3 RCT THRIVE-AA2	517	CTP-543 12 mg, 2id	SALT ≤ 20% week 24	38.3%
			CTP-543 8 mg, 2id		33%
			Placebo, 2id		0.8%
Oral ritlecitinib and brepocitinib[50]	Phase 2a RCT ALLEGRO	142	Ritlecitinib 200 mg/day, then 50 mg/day	$SALT_{30}$ week 24	50%
			Brepocitinib 60 mg/day, then 30 mg/day		64%
			Placebo, 1id		2%
Oral ritlecitinib[52,53]	Phase 2b/3 RCT ALLEGRO	718	Ritlecitinib 200 mg/day, then 50 mg/day	SALT ≤ 20% week 24	30.6%
			Ritlecitinib 200 mg/day, then 30 mg/day		22.3%
			Ritlecitinib 50 mg/day		23.4%
			Ritlecitinib 30 mg/day		14.3%
			Ritlecitinib 10 mg/day		1.7%
			Placebo, 1id		1.5%
Topical ruxolitinib[46]	Phase 2 RCT	78	Ruxolitinib 1.5%, 2id	$SALT_{50}$ week 24	12.8%
			Vehicle, 2id		12.8%
Topical delgocitinib[47]	Phase 2 RCT	31	Delgocitinib 30 mg/gm, 2id	$SALT_{50}$ week 12	11.8%
			Vehicle, 2id		16.7%

RCT: randomized clinical trial; SALT: severity of alopecia tool; $SALT_n$: ≥ *n*% improvement from baseline SALT score.

≤ 20%) showed that the proportion of patients with ≥ 80% hair regrowth in BRAVE-AA1 was 38.8, 22.8, and 6.2%, respectively, in the 4 and 2 mg, and placebo groups, while in BRAVE-AA2 it was 35.9, 19.4, and 3.3%, respectively (Table 1). These results were considered statistically significant *($p < 0.001$),* and oral baricitinib

was considered effective and also safe in the treatment of AA, with mostly mild adverse events at rates similar to placebo[31].

Positive results from the BRAVE-AA1 and BRAVE-AA2 studies led the Food and Drug Administration (FDA) to approve oral baricitinib (Olumiant) for the treatment of AA on 13th June 2022[32]. As such, baricitinib is the first and only approved treatment for AA, marking an important milestone in the history of the disease, with a major impact on patients with severe AA[10]. Oral baricitinib is recommended for patients with severe AA at a dose of 2 mg/day, which may be increased to 4 mg/day if clinical response is inadequate. An initial dose of 4 mg/day may be considered in patients with AT/AU or with significant loss of eyelashes and/or eyebrows[26]. Before starting therapy, it is recommended to exclude the presence of tuberculosis and other active infections (hepatitis B and C and human immunodeficiency virus infection), and patients should be monitored for signs and symptoms of infection throughout treatment[32]. In addition, patients should undergo hematologic monitoring before and during treatment, including a complete blood count, coagulation studies, and a comprehensive metabolic panel. Moreover, they are contraindicated during pregnancy or breastfeeding, there is little safety data for young children, and lower dose limits are recommended for older individuals[26].

Oral tofacitinib

Tofacitinib, the first to be developed, is a first-generation JAK inhibitor and the least selective, inhibiting all JAK enzymes (pan-JAK), although it has a preference for JAK1 and JAK3[6,10]. The efficacy of oral tofacitinib was first suggested in 2014 in a case report of a patient with universal AA and concomitant plaque psoriasis treated with tofacitinib 15 mg/day, who experienced regrowth of all scalp hair at 3 months and all body hair at 8 months of treatment[33].

Multiple studies have demonstrated the efficacy and safety of tofacitinib in AA, but most are low-quality studies such as case reports and case series, with a few retrospective studies and single-arm clinical trials[10,26,34].

In 2016, an open-label, single-arm, clinical trial of tofacitinib 5 mg twice daily (2id) for 3 months in 66 patients with severe AA showed that 32% of patients were strong responders, with an improvement in baseline SALT score ≥ 50% (Table 1). Treatment was well tolerated, with limited adverse effects. However, 3 months after stopping tofacitinib therapy, all 20 responders had hair loss[35].

More recently, a systematic review and meta-analysis showed that oral tofacitinib is an effective and well-tolerated drug in the treatment of AA. Longer treatment (> 6 months) was associated with a greater ≥ 50% SALT score improvement from baseline response ($SALT_{50}$) in 62% of patients overall. Nevertheless, 3 months after tofacitinib discontinuation, most patients (74%) experienced a recurrence of AA, suggesting that the off-therapy clinical response is not durable[36].

Oral ruxolitinib

Ruxolitinib is a first-generation JAK inhibitor that preferentially inhibits JAK1 and JAK2, similar to baricitinib[26]. The efficacy of oral ruxolitinib in the treatment of AA was first suggested in 2014 in a clinical trial of three patients with moderate to severe AA who showed almost complete hair regrowth after 3–5 months of ruxolitinib 20 mg 2id[37].

Since then, several studies have been published demonstrating the efficacy and safety of oral ruxolitinib. In 2019, an open-label, comparative clinical trial was conducted with 75 patients with severe AA receiving either ruxolitinib 20 mg 2id or tofacitinib 5 mg 2id for 6 months. At the end of treatment, 84.2% of ruxolitinib patients and 78.4% of tofacitinib patients achieved a $SALT_{50}$ response (Table 1). Both drugs were well tolerated. However, after 3 months of follow-up, about two-thirds of patients showed signs of relapse with hair loss[38].

More recently, a deuterated form of ruxolitinib, deuruxolitinib (CTP-543), has been developed and evaluated in high-quality trials. The first study, a phase 2, double-blind, placebo-controlled RCT, involved 149 patients with severe AA divided into four groups—placebo, 4, 8, and 12 mg CTP-543 2id[39]. The proportion of patients achieving a $SALT_{50}$ response after 24 weeks was defined as the primary outcome. At the end of the study, the proportion of patients with a $SALT_{50}$ response was statistically significantly higher in the CTP-543 8 mg (47%) and 12 mg (58%) than in the 4 mg (21%) and placebo (9%) groups ($p < 0.001$) (Table 1). Adverse reactions observed were similar in all groups and were mostly mild to moderate[39].

Therefore, the 8 and 12 mg doses of oral CTP-543 2id were selected to test its efficacy and safety in two phase 3 RCTs operated on a larger scale. The studies termed THRIVE-AA1 and THRIVE-AA2 enrolled 706 and 517 patients, respectively, who received CTP-543 12 mg, CTP-543 8 mg, or placebo 2id for 24 weeks[40]. The primary outcome in both studies (proportion of patients with a SALT score ≤ 20%) at 24 weeks of treatment

showed ≥ 80% hair regrowth in THRIVE-AA1 in 41.5% in the 12 mg group, 29.6% in the 8 mg group, and 0.8% in the placebo group, whereas in THRIVE-AA2 it was 38.3, 33, and 0.8%, respectively (Table 1). In both studies, CTP-543 8 and 12 mg was statistically significant compared to placebo ($p < 0.0001$). Overall, CTP-543 was well tolerated and demonstrated a good safety profile[40,41].

The positive results from these high-quality studies suggest that oral CTP-543 may be the next JAK inhibitor to be approved for the treatment of AA in the near future[10].

Side effects of oral JAK inhibitors

As noted throughout this paper, oral JAK inhibitors appear to be safe and well-tolerated drugs for the treatment of AA. The most common adverse reactions are mild and include infections, such as upper respiratory infections, urinary infections, and folliculitis; diarrhea; acne; and headache[42]. Laboratory changes such as cytopenias, elevated low-density lipid and high-density lipid cholesterol, transaminases, and creatinine kinase have also been described but were overall uncommon and transient[6,9,31,36]. Herpes zoster infection is rare but has been observed in some studies[31,36].

However, in the treatment of other inflammatory diseases, such as rheumatoid arthritis, where the safety profile of oral JAK inhibitors has been more extensively studied, their use has been associated with an increased risk of serious infection, thromboembolic and major adverse cardiovascular events, and cancer[43,44]. As a result of these findings, in September 2021, the FDA issued a "black box warning" for JAK inhibitors, the highest level of warning of all, to alert patients to the potentially serious risks associated with these drugs, mostly related to their potent immunosuppressive effects[10,26,45]. More recently, in October 2022, the European Medicines Agency's safety committee (Pharmacovigilance Risk Assessment Committee) recommended further limitations on the use of JAK inhibitors in individuals aged 65 years or above, those at increased risk of cancer, major cardiovascular problems and deep vein thromboembolism, and current smokers or former long-term smokers[46].

Still, to date, the various clinical trials conducted in AA suggest that oral JAK inhibitors appear to have a low risk of serious adverse events in this specific population, but long-term data is still not available. In addition, this may be explained by the fact that AA patients are generally younger and healthier, lower doses are used, and AA does not affect patients' health as much as in other diseases where JAK inhibitors are used[26,36]. In any case, it is mandatory to warn patients about the potential risks associated with the use of oral JAK inhibitors and to monitor them throughout their treatment[10,36].

Topical JAK inhibitors

Janus kinase (JAK) inhibitors have begun to be tested in topical formulations for the treatment of AA to limit systemic absorption and potential side effects of the oral route[4,26]. In 2020, a phase 2, double-blind, vehicle-controlled RCT evaluated the efficacy of topical ruxolitinib 1.5% 2id in 78 patients with moderate AA for 24 weeks. At the end of this period, only 5 of 39 patients in both the ruxolitinib and vehicle groups achieved a $SALT_{50}$ response, leading to the conclusion that topical ruxolitinib has no significant effect in patients with AA (Table 1)[47]. Later, another phase 2 RCT demonstrated that topical delgocitinib (a pan-JAK inhibitor) 30 mg/gm 2id was not effective in the treatment of moderate to severe AA, as there was no statistically significant difference in SALT score reduction between the delgocitinib group and the vehicle group after 12 weeks of treatment (Table 1)[48].

Recent meta-analyses and systematic reviews have also shown that topical JAK inhibitors are not effective in the treatment of AA[42,49]. In addition, topical JAK inhibitors appear to be even less effective than these reviews suggest, as approximately 50% of clinical trials of topical JAK inhibitors were terminated prematurely due to lack of efficacy or by sponsor decision, and their results were not published. Thus, these meta-analyses may have been subject to publication and selection bias, which could have been avoided by including the grey literature[50].

Second-generation JAK inhibitors

Second-generation JAK inhibitors, which are more selective in their action, were developed with the goal of reducing the side effects of inhibiting multiple pathways[34]. There are four second-generation JAK inhibitors being studied for the treatment of AA–ritlecitinib, brepocitinib, upadacitinib, and abrocitinib[10].

Oral ritlecitinib, an inhibitor of JAK3 and tyrosine kinase expressed in hepatocellular carcinoma, and oral brepocitinib, an inhibitor of JAK1 and TYK2, have been shown to be effective in the treatment of AA in a double-blind, placebo-controlled RCT named ALLEGRO. In the phase 2a study, 142 patients with severe AA were divided into three groups–ritlecitinib (200 mg/day for 4 weeks and 50 mg/day for the remaining 20 weeks), brepocitinib

(60 mg/day for 4 weeks and 30 mg/day for the remaining 20 weeks) and placebo for 24 weeks[51]. After this treatment period, the proportion of patients achieving ≥ 30% SALT score improvement from baseline response ($SALT_{30}$) was significantly higher in the ritlecitinib (50%) and brepocitinib (64%) groups than in the placebo group (2%) (Table 1). Overall, the drugs were well tolerated. However, two patients experienced a serious adverse reaction to brepocitinib[51]. In addition, after treatment discontinuation, patients experienced significant hair loss requiring therapy reintroduction within a medium of 16 weeks in the ritlecitinib group and 24 weeks in the brepocitinib group[52]. These positive results led to the initiation of the ALLEGRO phase 2b/3 study with ritlecitinib alone, which enrolled 718 patients with severe AA. At the end of 24 weeks of treatment, a statistically significant larger proportion of patients receiving the highest doses of ritlecitinib (30 or 50 mg/day, with or without a loading dose of 200 mg/day for 4 weeks) achieved a SALT score of≤ 20% compared to placebo (Table 1)[53,54]. The safety profile of ritlecitinib was consistent with previous studies. There is great interest in this drug because it is the only one that avoids JAK1 and JAK2 inhibition and their potential side effects (increased cholesterol and transaminases and cytopenias)[55].

Upadacitinib and abrocitinib, both JAK-1 inhibitors used in atopic dermatitis, have less scientific evidence in the treatment of AA, with only a few case reports demonstrating efficacy[10,26]. Higher quality clinical trials will be needed in the future to understand the true role these 2 JAK inhibitors may play in the treatment of AA[10].

Limitations of JAK Inhibitors

Although oral JAK inhibitors have proven to be an excellent therapeutic option in the treatment of AA, there are some limitations that must be considered.

First, as several studies have shown, after discontinuation of JAK inhibitors, AA rapidly relapses, and patients experience hair loss again[35,38,51,56,57]. This suggests that continuous treatment with these drugs is necessary to achieve a sustained off-therapy clinical response in AA[6,8,22].

In addition, another concern with the use of JAK inhibitors in the treatment of AA is their high cost, which can reach $50,000/year per patient in the United States. This is much higher than any other treatment currently used for AA and may be unsustainable for the healthcare system, especially if JAK inhibitors have to be taken chronically[6].

Phosphodiesterase-4 inhibitors (iPDE4)

Phosphodiesterase-4 inhibitors (iPDE4) are small molecules that prevent the hydrolysis and inactivation of cyclic adenosine monophosphate, thereby limiting the production of several pro-inflammatory cytokines[58]. Oral apremilast is an iPDE4 that has gained interest as a potential novel therapy in AA, as it has shown efficacy in some case reports[59].

However, more recently, oral apremilast failed to demonstrate efficacy in the treatment of AA in a phase 2 RCT. In this study, 30 patients with severe AA were randomized to receive apremilast 30 mg or placebo 2id for 24 weeks. At the end of treatment, only one patient in each group achieved a $SALT_{50}$ response, and there was no statistically significant difference in SALT score improvement between the apremilast and placebo groups (p = 0.38) (Table 2)[57]. These negative results corroborated the findings of a case series in which oral apremilast also demonstrated a lack of efficacy in the treatment of severe AA[60].

Biologics

In recent years, several biologics approved for the treatment of other inflammatory diseases have been tested as therapeutic options in AA, most notably dupilumab, secukinumab, and aldesleukin.

Dupilumab is a human monoclonal antibody approved for the treatment of moderate to severe atopic dermatitis that blocks the alpha subunit of the IL-4 receptor (IL-4R), thereby inhibiting two major Th2 cytokines, IL-4 and IL-13[61]. As mentioned above, the Th2 axis may play a pathogenic role in AA[23,60]. In addition, epidemiologic studies have shown a strong association between AA and atopic dermatitis, providing a therapeutic rationale for the use of dupilumab in AA[62]. However, the results of dupilumab in the treatment of AA are paradoxical. A recent systematic review showed that, on the one hand, 23 AA patients showed significant hair growth with dupilumab, but on the other hand, 21 were diagnosed with AA or had their preexisting AA worsened after treatment with dupilumab[63]. Amplification of the Th1 response resulting from inhibition of the Th2 axis has been hypothesized as the reason for this contradictory effect of dupilumab[9].

More recently, a phase 2a RCT was conducted with 60 patients with moderate to severe AA who received weekly subcutaneous injections of 300 mg dupilumab or placebo[60]. At the end of 24 weeks of treatment, 10% of patients in the dupilumab group achieved a $SALT_{49}$ response,

Table 2. Summary of the main studies conducted with phosphodiesterase-4 inhibitors and biologics in the treatment of AA

Drug	Study type	Nº of patients	Dosing	Primary outcome	Response (%)
Oral apremilast[57]	Phase 2 RCT	30	Apremilast 30 mg, 2id	$SALT_{50}$ week 24	8.3%
			Placebo, 2id		12.5%
Subcutaneous dupilumab[60]	Phase 2a RCT	60	Dupilumab 300 mg, weekly	$SALT_{50}$ week 24	10%
			Placebo, weekly		0%
Subcutaneous secukinumab[63]	Phase 2 RCT	11	Secukinumab 300 mg weekly, then monthly	$SALT_{50}$ week 24	0%
			Placebo weekly, then monthly		0%
Subcutaneous aldesleukin[64]	Phase 2 RCT	43	Aldesleukin at low doses, four cycles	$SALT_{50}$ at 52 weeks follow-up	14.3%
			Placebo, four cycles		9.1%

RCT: randomized clinical trial; SALT: severity of alopecia tool; $SALT_n$, ≥ *n*% improvement from baseline SALT score.

compared with none in the placebo group (0%) (Table 2). In addition, patients with serum immunoglobulin E (IgE) levels ≥ 200 IU/ml and/or a personal or family history of atopy demonstrated a superior clinical response, suggesting that serum IgE measurement may be predictive of treatment response and aid in patient selection. The adverse effects observed were mostly mild[61]. Overall, the results of this clinical trial demonstrated the potential efficacy of dupilumab in the treatment of AA.

Secukinumab is a human IL-17A antagonist being investigated for the treatment of AA based on the potential pathogenic role of the Th17 axis in the pathophysiology of the disease[23,64]. In the only RCT conducted, 11 patients with severe AA were randomized to receive subcutaneous injections of 300 mg secukinumab or placebo, and none of the 11 patients achieved a $SALT_{50}$ response at the end of treatment (Table 2). Based on these results, secukinumab was shown to be ineffective in the treatment of AA[63].

Aldesleukin is a recombinant IL-2 that, at low doses, promotes the expansion and suppressive function of regulatory T cells, deficient in AA[15,65]. In a pilot study of 5 patients with severe refractory AA, partial hair regrowth was observed in 4 patients after administration of low-dose aldesleukin[66]. This led to an RCT of 43 patients with severe AA treated with the same dose of aldesleukin subcutaneously[64]. However, after 52 weeks of follow-up, no statistically significant difference was observed in the proportion of patients achieving the $SALT_{50}$ score between the aldesleukin group and the placebo group (14.3 vs 9.1%, respectively) (Table 2). Thus, it can be concluded that low-dose aldesleukin does not appear to be an effective monotherapy for the treatment of severe AA[64].

Conclusion

Alopecia areata (AA) is a chronic disease with an unpredictable nature that has a very negative impact on the quality of life of patients, with no curative treatment available yet. However, recent advances in understanding the pathophysiology of AA have led to a revolution in therapeutic options for AA. Available treatments have evolved from nonspecific immunosuppressive drugs with many systemic side effects to pathobiology-based drugs with improved specificity in their therapeutic targets and better safety profiles. At the forefront of these innovative treatments are JAK inhibitors, with oral baricitinib (Olumiant) being the first and only drug ever approved for the treatment of AA. In the coming years, more oral JAK inhibitors are expected to be approved for the treatment of AA, such as CTP-543 and ritlecitinib, which have shown efficacy and safety in a large, randomized phase 3 clinical trials.

Despite the fantastic opportunity in the treatment of AA that the advent of JAK inhibitors has brought, there are some concerns about their use that need to be addressed. JAK inhibitors are expensive drugs, which is set to remain one of the biggest barriers to their use in clinical practice.

In addition, patients do not show a sustained off-drug clinical response after discontinuation of JAK inhibitors, so long-term therapy seems to be necessary to maintain response. Given that this therapy may be administered indefinitely, further studies are needed in the future to assess the long-term safety of oral JAK inhibitors. Transitioning these patients to long-term regimens with second-generation oral JAK inhibitors or topical JAK inhibitors is an alternative that should be explored, as they appear to have less potential for systemic side

effects. However, topical JAK inhibitors studied until now have shown to be ineffective in the treatment of AA. Therefore, it might be important to find ways to improve the skin penetration of these drugs so that they can still play a role in the treatment of AA. Oral second-generation generation JAK inhibitors, on the other hand, have demonstrated efficacy in clinical trials and are expected to be added to the AA therapeutic armamentarium soon.

Other innovative treatments, such as phosphodiesterase-4 inhibitors and biologics, appear to have more limited efficacy in the treatment of AA. Among these, dupilumab stands out as being more effective than the others, especially in patients with atopic features. However, further studies are needed to clarify its potential paroxysmal effects on AA.

In the coming years, as more of the pathophysiological mechanisms of AA are unveiled, the number of therapeutic options available to treat this very challenging disease is expected to grow significantly.

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Conflicts of interest

None.

Ethical disclosures

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

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REVIEW ARTICLE

Penile carcinoma: what dermatologists need to know

Carcinoma do pénis: o que os dermatologistas devem saber

Maria J. Guimarães[1,a], Rita Macieira[2], Filomena Azevedo[3], and Carmen Lisboa[2,3]*

[1]Department of Dermatology and Venereology, Hospital de Braga, Braga; [2]Microbiology, Department of Pathology and Centre for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University of Porto, Porto; [3]Department of Dermatology and Venereology, Centro Hospitalar Universitário de São João, Porto, Portugal

[a]ORCID: 0000-0002-3247-2470

Abstract

Penile cancer is a rare disease in developed countries and is frequently underrecognized by clinicians leading to delays in diagnosis and treatment. Squamous cell carcinoma (SCC) is the predominant pathological entity, representing 95% of all penile cancers. The most important risk factor for penile SCC is human papillomavirus (HPV) infection, with an estimated prevalence of 50%. Other major risk factors include phimosis, chronic inflammatory dermatosis, and poor genital hygiene. Two major pathophysiologic pathways have been proposed, one linked to HPV and another to chronic inflammation. Penile SCC usually presents as an erythematous area of induration or an ulcerating lesion, although changes can be more subtle in premalignant lesions [PeIN]. Confirmation of the diagnosis by biopsy and histopathological examination should be followed by staging. For localized diseases, namely PeIN, topical immunotherapy, chemotherapy, and epithelial ablative techniques are treatment options. For localized SCC, the mainstay of treatment is complete excision. Radiotherapy can be considered an organ-sparing alternative. The role of chemotherapy in penile SCC remains under discussion. The estimated 5-year overall survival is 66%, varying from 90% for T1N0M0 tumors to < 50% for patients with positive lymph nodes. Clarification of the role of HPV in premalignant lesions and penile SCC pathology has the potential to improve prevention and treatment regimens, namely through vaccination against HPV. Given its rarity and low levels of awareness by both patients and clinicians, penile SCC represents a diagnostic challenge. Prompt diagnosis is key to effective treatment since prognosis in the early stages is excellent.

Keywords: Penile Cancer. Penile carcinoma. Penile intraepithelial neoplasia. HPV.

Resumo

O carcinoma do pénis é raro em países desenvolvidos e frequentemente subestimado, levando a atrasos no diagnóstico e tratamento. O carcinoma espinocelular (CEC) é a entidade patológica predominante, representando 95% das neoplasias penianas. O fator de risco mais importante para o CEC peniano é a infeção pelo papilomavírus humano (HPV), com uma prevalência estimada de 50%. Outros fatores de risco incluem fimose, dermatose inflamatória crónica e má higiene genital. Foram propostas duas vias etiopatogénicas principais, uma ligada ao HPV e outra à inflamação crónica. Clinicamente, o CEC peniano surge como uma área eritematosa endurecida ou ulcerada, embora em lesões pré-malignas (PeIN) as alterações possam ser mais subtis. A confirmação do diagnóstico por biópsia e exame histopatológico deve ser seguida de estadiamento. A base do tratamento na doença localizada é a excisão cirúrgica completa e nas lesões pré-malignas a imunoterapia ou técnicas ablativas locais.A radioterapia pode ser considerada como uma alternativa poupadora de órgão. O papel da quimioterapia no CEC peniano

***Corresponding author:**
Maria J. Guimarães
E-mail: mjcunhaguimaraes@gmail.com

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permanece em discussão. A sobrevida global estimada aos 5 anos é de 66%, variando de 90% para tumores T1N0M0, a menos de 50% para doentes com metástases ganglionares. A clarificação do papel do HPV nas lesões pré-malignas e no CEC peniano tem potencial para melhorar os regimes de prevenção e tratamento, nomeadamente através da vacinação contra o HPV. Considerando a raridade e falta de consciencialização por doentes e médicos, o CEC peniano representa um desafio diagnóstico. O diagnóstico precoce é fundamental uma vez que o prognóstico é excelente em estadios iniciais.

Palavras-chave: Cancro do pénis. Carcinoma do pénis. Neoplasia intraepitelial do pénis. Infeção por HPV.

Introduction

Despite its rising incidence in most European countries over the last decade, penile cancer is still considered a rare disease[1]. It is frequently underrecognized by clinicians leading to delays in diagnosis and treatment[2,3]. Additional reasons for delaying diagnosis are attributed to patient factors, as usually, patients defer seeking medical advice due to mild symptoms, feelings of embarrassment, guilt, fear, denial, and lack of awareness[1,4]. It is estimated that 15 to 60% of patients postpone clinical observation for at least 1 year after the first signs of the disease[2]. This underlines the importance of consciousness regarding the condition, particularly for dermatologists and urologists most sought by the patient for these lesions. Prompt diagnosis is key for appropriate and early treatment, reducing the morbidity and mortality from penile cancer.

Squamous cell carcinoma (SCC) is the predominant pathological entity, representing 95% of all penile cancers. The estimated 5-year overall survival is 66%[5]. Delay in diagnosis impacts prognosis[1].

Epidemiology

Penile SCC had a global estimated burden of 36,068 cases in 2020[3]. Incidence rates have marked geographical variability[2,5,6]. Whereas the prevalence in developed countries is less than < 1/100,000, it can reach 10% of all cancers in men in low and middle-income regions, explained by many social, hygienic, and cultural factors[3,4,7]. In developed countries, namely in Europe, a rise in penile cancer incidence has been reported[7]. Penile SCC usually occurs in men aged between 50 and 70 years[1,8]. Nevertheless, it can also occur in younger patients, especially if associated with HPV[1,7].

Risk factors

The most important risk factor for penile cancer is HPV infection, especially by oncogenic subtypes, such as HPV 16 or 18 and eventually 31, 33, 45, 56, and 65[9]. HPV prevalence is estimated at around 50%[9], and the relative risk for penile cancer is approximately 4.5 higher in HPV-seropositive patients[10]. However, the impact of HPV infection on penile cancer diagnosis, prognosis and prevention still warrants further research.

Although genital warts are generally associated with infection with low-risk HPV types, premalignant and malignant lesions have been found within genital warts[11,12]. Genital warts can constitute risk markers for the development of other HPV infections, as they indicate high-risk sexual behaviors[10]. Thus, close follow-up of patients with sexually transmitted infections (STIs), namely anogenital warts, should be considered to assess the risk of developing malignant lesions.

Besides a history of STIs, other major risk factors for penile cancer include phimosis, chronic inflammatory dermatoses such as lichen sclerosus, poor genital hygiene, ultraviolet A phototherapy, obesity, smoking, immunosuppression, low socioeconomic status, and low educational level[13,14].

Basically, two major pathogenic pathways have been proposed, one linked to HPV and another linked to chronic inflammation[1,6]. Based on this, the 2022 World Health Organization classification recommends the subdivision of penile SCC into HPV-dependent and HPV-independent types[15]. This classification recognizes an association between histological variants and HPV: basaloid, papillary-basaloid, warty, warty-basaloid, clear cell and lymphoepithelioma-like carcinomas are considered HPV related; common type, carcinoma cuniculatum, verrucous, papillary, pseudohyperplastic, pdeudoglandular, adenosquamous and sarcomatoid carcinomas are considered HPV-independent[5,15,16]. However, diagnosis based solely on morphological criteria may be misleading in a small proportion of tumors, and HPV deoxyribonucleic acid (DNA) testing and/or p16 immunostaining is required to classify SCC as HPV-associated or HPV-independent[5] properly. The expression of p16 is correlated with the integration of HPV's viral genome into the intracellular host genome[17]. Therefore, currently, p16 expression found in penile intraepithelial neoplasia (PeIN) or invasive SCC is considered a surrogate marker for high-risk HPV infection[17,18]. Additionally, the role of p16 as a prognostic marker is currently under investigation, as some works have shown that men with HPV or p16-positive penile cancer have a survival advantage[17,18].

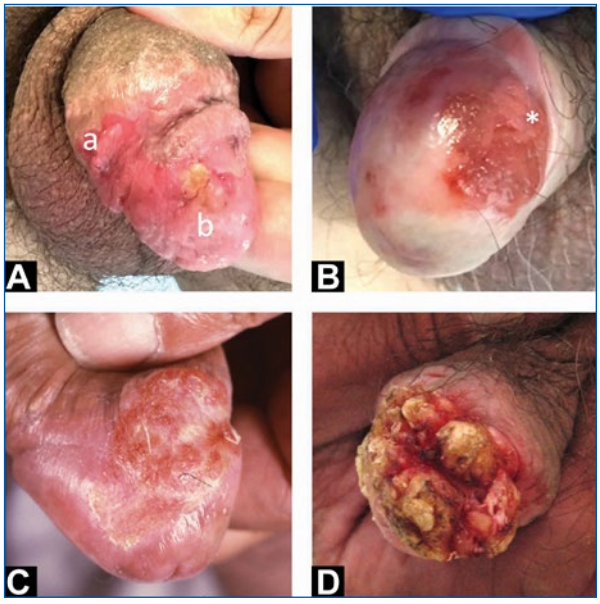

Figure 1. A: erythematous infiltrated plaque corresponding to PeIN 2 (a) and invasive SCC (b); **B:** erythroplasia of Queyrat (SCC *in situ*) with an area (*) of invasive SCC; **C:** area of induration in a patient with lichen sclerosus, corresponding to invasive SCC; **D:** invasive SCC manifested by a verrucous exophytic lesion distorting normal anatomy of glans and prepuce. PeIN2: penile intraepithelial neoplasia grade 2; SCC: squamous cell carcinoma.

Precursor lesions and HPV

Penile intraepithelial neoplasia (PeIN), a precursor lesion for penile cancer, is usually classified according to the degree of dysplasia, namely PeIN I if mild dysplasia is present, PeIN II in moderate dysplasia and PeIN III when dysplasia is severe or carcinoma *in situ*[19]. Like SCC, PeIN can also be classified as HPV-related or non-related[15]. Although these lesions are clinically similar, the association with HPV can be relevant as it could potentially guide treatment and enhance follow-up strategies. The pooled HPV DNA prevalence in PeIN was 79.8%[19], higher than its prevalence in invasive SCC, suggesting that HPV infection may be associated with a less aggressive evolution and with a more predictable carcinogenic path[20].

Clinical aspects

Around > 50% of penile SCC arises in the glans, followed by the prepuce, both glans and prepuce, coronal sulcus and the shaft[2]. Clinical presentation can vary, but SCC usually manifests as an erythematous area of induration or an ulcerating infiltrative lesion (Fig. 1)[16]. In premalignant lesions, changes can be more subtle, such as an erythematous patch with variable degrees of infiltration (Fig. 2)[16]. Bowenoid papulosis, Bowen's disease and erythroplasia of Queyrat are three clinically recognized manifestations of carcinoma *in situ*[21]. The former is characterized by multiple red-brown papules, sometimes coalescing into a plaque. Bowen's disease presents as a pink plate with white scales, and erythroplasia of Queyrat manifests as an eroded erythematous plaque with well-demarcated borders usually arising in the glans or prepuce[21]. Early suspicion and biopsy are necessary to prevent delays in diagnosis and treatment[1]. This is particularly relevant in patients with chronic genital dermatosis, like lichen sclerosus. Faced with a persistent suspicious lesion, particularly one with little or no response to corticosteroids, one should have a low threshold to perform a biopsy[16].

Diagnosis and staging

Confirmation of the diagnosis by biopsy of the suspected lesion and histopathological examination should be followed by staging[1]. Penile SCC should preferably be staged according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) eighth edition tumor, nodes, and metastases classification (Table 1).

Physical examination should include inguinal LN palpation[16]. In obese patients, the limitations of clinical evaluation can be overcome through ultrasound examination of inguinal LN[6]. When enlarged, LN is detected on physical examination; LN metastases can be diagnosed by percutaneous fine-needle aspiration cytology[4].

In clinically unremarkable inguinal LNs, management is particularly challenging because, in up to 25% of cases, inguinal lymphatic micrometastases are present[1,6]. In these cases, a dynamic sentinel node biopsy (DSNB) is recommended in intermediate (T1G2) or high-risk (T1G3 or worse) disease[4]. The sensitivity of DSNB is approximately 90-95% for micrometastases detection, with low associated morbidity[6]. In centers where DSNB is not available, modified inguinal lymphadenectomy is a safe and appropriate alternative[6,22].

When positive LN is detected, staging for systemic metastases is recommended through computed tomography of the thorax, abdomen, and pelvis[16]. A positron emission tomography scan is an acceptable alternative with high sensitivity and specificity in the detection of

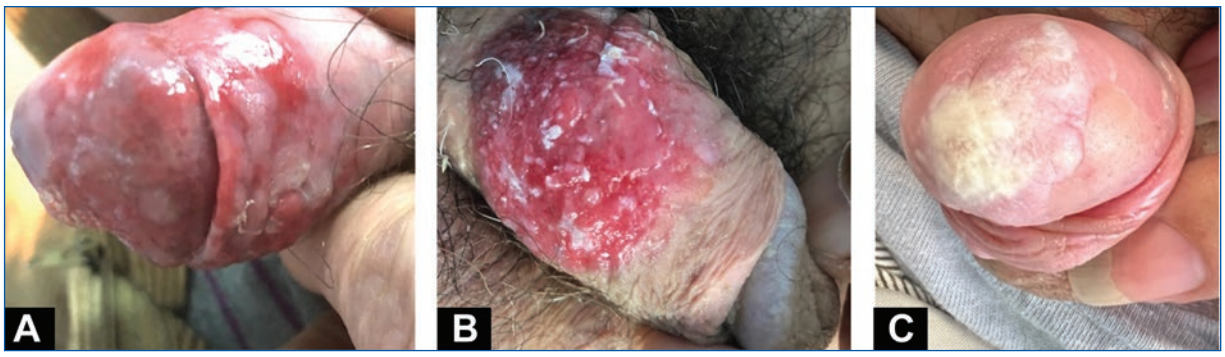

Figure 2. A: erythematous patch corresponding to SCC *in situ* (Erythroplasia of Queyrat); **B:** SCC *in situ* on penile shaft; **C:** verrucous whitish patch on glans corresponding to SCC *in situ*. SCC: squamous cell carcinoma.

distant metastases; however, limited spatial resolution reduces its acuity for small metastases. Additionally, false positives may occur due to inflammation[23].

Treatment

Given the lack of randomized controlled trials, multidisciplinary care in experienced centers is crucial for improving outcomes[16].

Previously, the mainstay of treatment in localized disease was excision with wide margins (2 cm)[1]. However, current recommendations allow narrow tumor margins as long as complete excision is achieved[1]. For carcinoma *in situ*, topical immunotherapy or chemotherapy (imiquimod applied once daily or on alternate days, 5-fluorouracil applied on alternate days for 6 weeks[24]), as well as epithelial ablative techniques (cryosurgery, CO_2 laser, neodymium-doped yttrium aluminum garnet laser or photodynamic therapy) are treatment options[1]. For low and intermediate-grade T1 lesions, circumcision, wide local excision or partial glansectomy are recommended[16]. However, high-grade T1 or T2-T3 disease requires more extensive surgical interventions, with partial or total penectomy[1,16]. Mohs surgery could play a role in smaller lower-grade tumors, achieving a superior esthetic and functional result[1,25]. Its use in larger, stage II or above tumors should be discouraged since these cases are not suitable for penile-sparing therapy[25].

Squamous cell carcinomas (SCCs) are generally radiosensitive tumors[1]. Thus, radiotherapy, particularly brachytherapy, can be considered an organ-sparing alternative[16]. This modality is reserved as the initial treatment for invasive T1 and T2 cancers. Despite local recurrence rates ranging to 20% after 5–10 years, secondary control could be achieved by salvage surgery in 85% of cases[4]. Radiotherapy is also advocated as an adjuvant treatment to the inguinal lymphatic area when histopathological examination reveals more than one metastatic LN or extranodal extension[4].

The role of chemotherapy in penile SCC remains under discussion, as most available evidence comes from small prospective or retrospective studies[4]. Further high-quality prospective studies are required. Cisplatin has been the cornerstone of the combination regimens used[4]. Neoadjuvant chemotherapy (NC) is recommended in patients with fixed or bulky inguinal LN, bilateral LN involvement, or pelvic node involvement[16]. Similarly, adjuvant chemotherapy is advocated for patients that had not received NC in pN2-pN3 disease[4,16].

Palliative therapy is the standard of care in patients with unresectable locally advanced or metastatic disease[16]. Studies show that palliative chemotherapy can achieve limited survival benefits[1].

Prognosis

The overall 5-year survival rates are above 90% for pT1 tumors, decreasing to 55% for pT3 and under 50% for patients with positive LN pN1-N3[1]. Patients with metastatic disease have a poor prognosis, with a median overall survival of 7–8 months[16]. Around > 90% of recurrences occur in the first 5 years, so patients should be carefully followed in this period, with follow-up visits every 3 months in the first 2 years and every 6 months in the remaining 3 years[4]. The recommended follow-up depends on nodal involvement, varying from physical examination alone to regular imaging, such as CT, MRI or ultrasound with fine needle cytology[1].

Table 1. AJCC/UICC 8th edition for clinical and pathological staging

Primary tumor (T)	
T-category	T criteria
Tx	Primary tumors cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma *in situ* (PeIN)
Ta	Noninvasive localized SCC
T1	Glans: tumour invades lamina propria Foreskin: Tumor invades dermis, lamina própria or dartos fáscia Shaft: Tumor invades connective tissue between epidermis and corpora
T1a	Without lymphovascular or perineural invasion and is not high grade (G3 or sarcomatoid)
T1b	With lymphovascular and/or perineural invasion or is high grade (G3 or sarcomatoid)
T2	Tumour invades corpus spongiosum with or without urethral invasion
T3	Tumour invades corpus cavernosum with or without urethral invasion
T4	Tumour invades adjacent structures (scrotum, prostate, pubic bone)
Regional nodes (N)	
Clinical N category	Clinical N criteria
cNx	Regional LNs cannot be assessed
cN0	No palpable or visibly enlarged inguinal LNs
cN1	Palpable mobile unilateral inguinal LN
cN2	Palpable mobile ≥ 2 unilateral inguinal LN or bilateral
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
Pathological N	Pathological N criteria
pNx	LN metastasis cannot be established
pN0	No LN metastasis
pN1	≤ 2 unilateral inguinal metastases, no extranodal extension
pN2	≥ 3 unilateral inguinal metastases or bilateral metastases, no extranodal extension
pN3	Extranodal extension of LN metastases or pelvic LN metastases
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis present
Histopathological grading (G)	
Gx	The grade of differentiation cannot be assessed
G1	Well-differentiated
G2	Moderately differentiated
G3	Poorly differentiated/high grade

AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control; T: primary tumor; SCC: squamous cell carcinoma; N: regional nodes; M: distant metastasis; G: histopathological grade of differentiation.

Future perspectives

The protective effect of HPV vaccination against cervical cancer is reported in various studies; however, in penile cancer, its impact is inconsistently described[26–28]. Vaccination in males is recommended by several international scientific societies and is now being implemented in many countries, including Portugal[29,30]. The impact of this preventive measure is promising and expected to be clarified in the next few years[31].

To improve early diagnosis, identify therapeutic targets and support prognosis evaluation; recent research has identified several tissue and serum biomarkers. Nevertheless, significant gaps still exist in understanding the potential clinical implications of each biomarker[8].

Several novel therapies are under investigation for the treatment of advanced-stage disease[16]. Phase II studies, including targeted therapies (e.g., EGFR inhibitors and immune checkpoint inhibitors), are ongoing with promising preliminary results[16]. A basic understanding of penile SCC at a molecular level holds promise in developing novel therapeutic approaches[16].

Conclusion

Given its rarity and low levels of awareness by both patients and clinicians, penile SCC represents a diagnostic challenge. Prompt SCC diagnosis is critical for effective treatment since prognosis in the early stages is excellent. Furthermore, clarification of the role of HPV in premalignant lesions and penile SCC pathology has the potential to improve prevention and treatment regimens.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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REVIEW ARTICLE

Vaccination in the setting of sexually transmitted infections consultation

Vacinação na consulta de infeções sexualmente transmissíveis

Lanyu Sun[1,a], Claúdia Brazão[1], Dora Mancha[1], Diogo de Sousa[1], and João Borges-Costa[1,2,3]*

[1]Service of Dermatology, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte; [2]Clínica Universitária de Dermatologia, Faculdade de Medicina da Universidade de Lisboa; [3]Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisbon, Portugal
[a]ORCID: 0000-0003-2148-1715

Abstract

Sexually transmitted infections (STIs) are a significant public health concern across the globe. Vaccines have played a crucial role in mitigating the burden of infectious diseases and are the most effective candidates for preventing STIs. Currently, vaccines for hepatitis A, hepatitis B virus (HBV), and human papillomavirus (HPV) are available. More recently, the smallpox vaccine was approved for Mpox (MPX) prevention. Ongoing research efforts are focused on developing vaccines for other STIs. This paper reviews the current indications for available vaccines for use in the context of STIs and discusses some of the vaccines currently being researched.

Keywords: Hepatitis A. Hepatitis B. Human papillomavirus. Mpox. Sexually transmitted infections. Vaccine.

Resumo

As infeções sexualmente transmissíveis (ISTs) são um importante problema de saúde pública em todo o mundo. Historicamente, as vacinas têm desempenhado um papel fundamental na redução das doenças infeciosas, sendo as melhores candidatas para a prevenção eficaz das ISTs. Atualmente, existem disponíveis as vacinas para a hepatite A, hepatite B e papilomavírus humano. Mais recentemente, a vacina contra a varíola foi aprovada para a prevenção da infeção por mpox. Para as outras ISTs, a investigação está em progresso para desenvolver uma vacina eficaz. Este artigo visa fazer uma revisão das indicações atuais das vacinas disponíveis para uso no contexto das ISTs e discutir algumas ISTs cujas vacinas que estão em investigação.

Palavras-chave: Hepatite A. Hepatite B. Vírus do papiloma humano. Mpox. Infeções sexualmente transmissíveis. Vacinas.

***Corresponding author:**
Lanyu Sun
E-mail: Lanyusun@gmail.com

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Introduction

The World Health Organization (WHO) reports that > 1 million STIs are acquired daily worldwide, with most individuals infected not experiencing any symptoms. STIs have a significant impact on sexual and reproductive health, leading to considerable health issues and economic costs globally. The highest incidence of STIs is associated with eight pathogens, of which four can be cured, namely syphilis, gonorrhea, chlamydia, and trichomoniasis, while the other four are incurable viral infections–HBV, herpes simplex virus (HSV), human immunodeficiency virus (HIV), and HPV[1].

Preventing and controlling STIs is a crucial public health priority. Common prevention strategies, such as comprehensive sex education and promoting condom use, may not be effective in the long-term due to the challenges of maintaining safe sexual behaviors. Vaccines have played a significant role in reducing the burden of infectious diseases, and they are now considered a crucial tool in STI prevention programs. The increasing rates of antimicrobial resistance, limited availability of new antibiotics, persistent viral STIs, and high rates of condomless sexual intercourse highlight the urgent need for effective STI vaccines. Currently, safe and effective vaccines are available for three viral STIs–HAV, HBV, and human HPV. More recently, the smallpox vaccine has also been approved for MPX prevention. Ongoing research is focused on developing vaccines against genital herpes and HIV, with several promising vaccine candidates in early clinical development. Further research is needed to develop vaccines for bacterial STIs such as chlamydia and gonorrhea[1].

This paper focuses on reviewing the current indications of the available vaccines to use in the setting of STIs and discussing some of the vaccine's ongoing research.

Hepatitis A

Hepatitis A virus (HAV) is responsible for causing approximately 1.4 million cases of infection globally each year. The primary mode of transmission is through the fecal-oral route, either through direct contact between individuals or through the consumption of contaminated food or water. HAV can also be transmitted through sexual activity, likely as a result of fecal-oral contact[2].

In low and middle-income countries, individuals are often exposed to the virus at an early age, resulting in a higher prevalence of immunization. Conversely, countries with higher levels of sanitation and socioeconomic conditions often have lower exposure to the virus, leading to a larger number of susceptible individuals. In developed countries, the number of infections is on the rise among high-risk groups, such as men who have sex with men (MSM). The main risk factors for HAV transmission in MSM include engaging in oral-anal and digital-anal intercourse, having multiple sexual partners, having current infections with other STIs, and visiting venues like gay saunas, dark rooms, and dating apps[3]. These factors increase the likelihood of exposure to the virus and subsequent infection.

Frequent outbreaks of HAV infection have been reported over the years. Between June 2016 and 2017, an unusual increase in cases of hepatitis A affecting mainly MSM has been reported in 22 countries of the European Union (EU)/European Economic Area (EEA), including Portugal.

In the United States (US), effective control of HAV among men who have MSM is achieved by including the HAV vaccine in childhood vaccination programs. However, in many other countries, such as Portugal, the HAV vaccine is not part of the routine vaccination schedule[4]. Vaccination is considered the most effective way to prevent HAV transmission among individuals at risk for infection who did not receive the HAV vaccine during childhood. Knowledge of HAV risks and prevention, including vaccination recommendations, is poor among affected MSM; indeed, there is still a low rate of vaccination among this population.

A study recently published in Lancet[5] suggests that, while reactive vaccination of MSM in England during future outbreaks could significantly reduce the outbreak's magnitude and be a cost-saving strategy, pre-emptive vaccination of MSM between outbreaks in sexual health services could save even more money and have a greater impact, if the preemptive vaccination rate is sufficiently high (9% vaccination rate per year among MSM attending Sexual Health Services for the 5 years prior to an outbreak) Thus, preemptive vaccination should be the preferred choice.

Since 1991, an inactivated HAV vaccine called Havrix has been licensed for use in Europe and approved for individuals aged 12 months and older. The vaccine is administered in two doses, given at 0 and 6–12 months apart (Table 1). Nearly all adults develop protective antibody levels within a month after the first dose, ranging from 94 to 100%, and 100% achieve protective levels after the second dose. Studies show that protective levels persist for over 40 years based on kinetic models of antibody decrease among adults. Additionally, a combined HAV and HBV vaccine called Twinrix has

been developed and licensed for use in adults aged 18 years and older who are at risk for HAV or HBV infections. The vaccine is given as a three-dose series on a 0, 1 and 6-month schedule and has equivalent immunogenicity to that of the monovalent hepatitis A vaccines[2].

The routine testing of prevaccination serologic for HAV immunity is not recommended. However, it is recommended to test for anti-HAV antibodies after vaccination for individuals whose clinical management depends on their immune status and those who may require revaccination, such as people with HIV infection and other immunocompromising conditions[2]. A protective antibody titer level is believed to be equal to or greater than 20 mIU/mL[3].

In case of recent exposure to HAV, individuals who have not been previously vaccinated should receive either a single dose of monovalent vaccine or immunoglobulin (IG) as soon as possible, preferably within 2 weeks after exposure. A monovalent vaccine is usually preferred over IG for postexposure prophylaxis (PEP) because it provides active immunity and longer-term protection, is easier to administer, and is more widely available and acceptable[2].

Hepatitis B

The number of newly diagnosed HBV infections reported from countries across Europe remains high, with most of these infections classified as chronic[4].

The primary way HBV is transmitted in Asia is perinatal, while in Africa, it is usually transmitted from one child to another. However, in industrialized countries such as Portugal, sexual activity is the most common mode of transmission for HBV. Engaging in unprotected sex with someone who is infected with HBV, having multiple sexual partners, being an MSM, having a history of other STIs, and using injection drugs are all factors that increase the risk of HBV infection in adolescents and adults. According to the 2020's report from the European Centre for Disease Prevention and Control (ECDC)[4], heterosexual transmission was the most common way that acute HBV infections were spread, followed by transmission among MSM.

In Portugal, the HBV vaccine has been included in the National Vaccination Plan (PNV) for all children. It is given in three doses, with the first dose administered at birth, the second dose at 1 month, and the third dose at 6 months. The vaccine is also recommended for adults who are at high-risk of HBV infection, such as healthcare workers, people who inject drugs, MSM, and individuals with chronic liver disease. The hepatitis B vaccine is generally well-accepted in Portugal, and vaccination coverage rates have been high, especially among children and adolescents. However, there are still some gaps in vaccine coverage, particularly among certain high-risk groups, and efforts are ongoing to increase access and uptake of the vaccine in these populations. Healthcare settings that offer STI services to adults at high-risk for infection should provide the hepatitis B vaccine to individuals who have not been vaccinated[2]. Simultaneous education of MSM about hepatitis A and B and routine use of dual HAV/HBV vaccine may help address attitudinal barriers that interfere with acceptance of vaccination. As universal hepatitis B vaccination of newborns and children becomes increasingly successful in the coming decades, the need for vaccinating individuals with specific risk factors will be significantly reduced[5].

There are two approved products for preventing HBV–the hepatitis B vaccine and hepatitis B immune globulin (HBIG). HBIG can provide temporary protection from HBV infection for a period of 3-6 months and is often used as PEP along with the hepatitis B vaccine. This is especially important for individuals who have not been previously vaccinated or have not responded well to vaccination[2].

The HBV vaccine is made using recombinant deoxyribonucleic acid (DNA) technology to produce hepatitis B surface antigen (HBsAg) in yeast, and it is effective for both preexposure vaccination and PEP.[3] The vaccine is available in Europe under the brand name Engerix-B®[2].

A positive immune response to the vaccine is defined as the development of HBV anti-HBs at a titer of > 10 mIU/mL after a complete and adequate immunization schedule measured preferably 1-3 months after the last vaccine administration[3]. In adolescents and healthy adults below 40 years of age, the percentage of individuals who develop a protective antibody response after the first dose of the HBV vaccine is approximately 30-55%, which increases to 75% after the second dose and to > 90% after the third dose. Studies have shown that vaccine-induced immune memory remains intact for > 30 years, and long-term protection against HBV infection persists despite a gradual decrease in anti-HBs antibodies over time[2].

Routine testing to determine antibody levels after hepatitis B vaccination is not needed for healthy individuals with normal immune systems, and booster doses are not recommended[2,3]. However, individuals with HIV infection should be tested for the presence of anti-HBs 1-2 months

after the third vaccine dose due to the possibility of impaired vaccine response. Postvaccination testing is also recommended for certain high-risk groups such as healthcare workers, sex, and needle-sharing partners of HBsAg-positive persons, immunocompromised individuals and hemodialysis patients. Individuals who have anti-HBs levels of < 10 mIU/mL after completing the primary hepatitis B vaccine series should undergo a new three-dose vaccine series and get tested for anti-HBs 1-2 months after receiving the third dose. If they still don't have protective antibody levels, they should undergo HBsAg and Anti-HBc testing to determine their HBV infection status[2].

Human papillomavirus (HPV)

Human papillomavirus (HPV) infection is the most frequent STI and the second most common cause of cancer attributable to an infectious agent globally[6].

The HPV is transmitted through skin-to-skin contact, which can lead to infection in susceptible people. Several studies reported a higher prevalence of HPV infection in MSM than in heterosexual men, especially in anal region[7,8].

Human papillomavirus (HPV) vaccines are generally considered safe and effective in preventing HPV infections and related health problems, such as anogenital warts and precancerous lesions. They are most effective when given to individuals who have not been previously exposed to HPV. When vaccination coverage is above 50%, there is substantial evidence of indirect protection, known as herd immunity, which can further reduce the spread of HPV infections in the population[6].

Three vaccines have been available since 2006—a bivalent vaccine containing HPV 16 and 18 genotypes, a tetravalent vaccine also containing HPV six and 11 genotypes, and a nonavalent vaccine, which contains genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58[3]. Only the bivalent and nonavalent HPV vaccines are currently available on the market in Portugal.

The WHO reports that only 30% of the target population worldwide has received the HPV vaccine. In Portugal, the nonavalent vaccine is included in the PNV and is given to both boys and girls at 10 years of age. It's also recommended for all individuals between the ages of 11 and 26. For adults aged 27-45, shared clinical decision-making is recommended to determine if vaccination is appropriate[2]. Certain high-risk groups, such as MSM, sex workers, people with multiple sex partners, and immunocompromised individuals [e.g. people living with HIV/acquired immunodeficiency syndrome (AIDS) (PLWH)], may benefit from the vaccine (Table 1). MSM, in particular, are at a high-risk of HPV infection and associated diseases and may not benefit from the girls-only vaccination programme. In England, MSM up to and including 45 years of age have been eligible for free HPV vaccination when they visit specialist sexual health services and HIV clinics since April 2018[9]. A recent study suggested that all MSM with HIV would benefit from nonavalent HPV immunization, especially those who are younger and have had prior gonococcal infections[10].

For individuals who start HPV vaccination before their 15th birthday, a two-dose schedule is recommended, with doses given at 0 and 6-12-month intervals. However, people who are 15 years of age or older or are immunocompromised should receive a three-dose schedule, with doses given at 0, 1-2, and 6-month intervals[2].

It's important to note that HPV vaccines should not be given to pregnant women, as the safety of these vaccines during pregnancy has not been established. However, the vaccines can be given to individuals regardless of their history of anogenital warts, abnormal Papanicolaou test or HPV test or anogenital precancer[2] (Table 1).

An updated systematic review and meta-analysis, which included data from 60 million individuals and up to 8 years of postvaccination follow-up, showed compelling evidence of the substantial impact of three-dose girls-only HPV vaccination programs with the quadrivalent or bivalent vaccines on infections by HPV 16 and 18 and HPV 31, 33, and 45 as a group, anogenital wart diagnoses, and CIN2+ [SB3] among women. Furthermore, the study also found evidence of herd effects among boys and older women[11].

According to ECDC, the nonavalent HPV vaccine is efficacious in preventing persistent HPV infection and cervical high-grade or worse lesions in females 16-26 years and in preventing persistent HPV infections, genital warts, and high-grade anal intraepithelial lesions among males 16-26 years. The data also suggest stronger immunogenicity of the nonavalent HPV vaccine against vaccine serotypes in males and females 9-15 years compared to females 16-26 years[12].

Mpox (MPX)

Currently, officially starting from May 2022, an outbreak of MPX is ongoing, with 82,474 cases being notified as of December 9. Around > 100 countries and territories are affected, from all six WHO regions[13].

Cases in the current outbreak present a spectrum of symptoms and signs that differs from that described in past outbreaks of MPX in endemic countries[14]. Most frequently reported differences include-no prodromal symptoms or very mild; rash appearing before prodrome; rash presenting with very few lesions and/or limited only in genital or perianal areas; and lesions that do not evolve synchronously[15].

Human-to-human transmission of MPX occurs when an uninfected individual comes in close contact with the skin lesions of an infected person, through respiratory droplets during prolonged face-to-face interaction, and *via* contaminated objects or surfaces (fomites). It is still unclear whether MPX can be transmitted through genital secretions. During the current outbreak, MPX DNA was found in seminal fluid samples of young adult male patients in Italy who reported having unprotected sex. However, further studies are required to determine if MPX can indeed be sexually transmitted through genital fluids. It's important to note that the mere presence of MPX nucleic acid in bodily fluids is not enough to confirm infectivity[15].

In the current outbreak in nonendemic countries, most of the cases have been detected in males between 18 and 50 years, primarily among MSM. Particular sexual practices have facilitated the transmission of MPX among MSM groups with multiple partners. A significant percent of the cases detected to date have been PLWH (39%) undergoing antiretroviral treatment. The impact of MPX infection on PLHW who are not on appropriate antiretroviral treatment in the at-risk groups could be higher[15]. Based on the evidence from the cases reported in the current outbreak, the likelihood of MPX spreading further in networks of people with multiple sexual partners in the EU/EEA is considered high and the likelihood of spreading among the broader population is assessed as very low[15]. The Modified Vaccinia Ankara-Bavarian Nordic or MVA-BN (marketed as Imvanex in Europe, Jynneos in the USA, and Imvamune in Canada) is a third-generation attenuated smallpox vaccine that was approved in Europe on 22 July 2022 for use against MPX[15]. According to older studies, it is estimated to be up to 85% effective in preventing MPX infection[16].

Preexposure phase III trials have demonstrated positive results for immunogenicity and indirect measures of efficacy; a favorable safety profile was confirmed for healthy population groups, as well as PLWH, people with atopic dermatitis and hematopoietic stem cell transplants[17]. The vaccine response among people with HIV with clusters of differentiation 4 cell count < 100 cells/m^3 has not been established[15].

Primary preventive vaccination is recommended for individuals at high-risk of exposure, including MSM or other individuals with multiple sexual partners and health workers at high-risk of exposure[17] (Table 1). PEP vaccination is recommended for close contacts of cases, prior to the onset of any symptoms, ideally within 4 days of first exposure (and up to 14 days in the absence of symptoms), to prevent the onset of disease or mitigate disease severity[17].

The MVA-BN is administered as a subcutaneous injection, preferably in the upper arm, with a two-dose regimen, with the second dose given at least 28 days after the first[15]. For adults who have been vaccinated against smallpox might only need one dose. Given the currently limited supply of the vaccine, intradermal injections, which only use one-fifth of the subcutaneous dose, were authorized by European Medicines Agency as a temporary measure to use while the supply of the vaccine remains limited[18].

The most common side effects (in more than one in 10 vaccinees) associated with the administration of MVA-BN were injection site reactions (pain, redness, swelling, induration, itching) and systemic reactions such as muscle pain, headache, fatigue, nausea, myalgia and chills. Persons with atopic dermatitis may experience more intense local skin reactions and other general symptoms, as well as a flare-up or worsening of their skin condition[17].

Some recent studies have shown the concrete efficacy of the MVA-BN vaccine in protecting against MPX. According to a study conducted in the US, males who had not received the Jynneos vaccine were found to have an MPX incidence rate that was 14 times higher than those who had received at least one dose of the vaccine ≥ 14 days earlier[19]. Another recent report by The UK Health Security Agency stated that after receiving a single dose of the MVA-BN smallpox vaccine, an individual could expect to have around 78% protection against MPX 14 days after vaccination[20].

Vaccines in development

Neisseria gonorrhoeae

Gonorrhea infections are common worldwide, with an estimated global burden of 87 million new cases in 2016. As multidrug-resistant strains of *Neisseria gonorrhoeae* (*N. gonorrhoeae*) become more prevalent and new antibiotics are in short supply, the need for an effective vaccine has become urgent[3]. Currently, there

is no vaccine available that targets *N. gonorrhoeae* directly. The development of a *N. gonorrhoeae* vaccine has been challenging, as the bacterium has a high degree of genetic variability, which allows it to evade the immune system. Moreover, *N. gonorrhoeae* lacks stable surface proteins, which are targets for most vaccines. Thus, efforts to develop a gonorrhoea vaccine have faced several obstacles. Despite the intense innate inflammatory response that is the hallmark of *N. gonorrhoeae*, there is no naturally acquired immunity to the bacteria, making it difficult to predict which types of response might be protective[21]. There are four current vaccine approaches—(1) meningococcal and gonococcal outer membrane vesicles (OMV) vaccines that are intrinsic self-adjuvants; (2) purified protein subunit vaccines; (3) mixed OMV and protein subunit vaccines and (4) immunotherapeutic vaccines that utilize adjuvants to stimulate Th1-specific immune responses[22].

Promising vaccine candidates are currently being evaluated in murine infection models with different adjuvants and antigen-delivery systems. The evaluation of vaccine candidates has been challenging because no correlates of protection have been identified against *N. gonorrhoeae* in humans[22].

Optimism about the feasibility of gonococcal vaccine development has been recently revived because of accumulating observational data related to vaccines developed for preventing the disease from *N. meningitidis* group B (MenB). There is mounting evidence suggesting that the vaccine to prevent MenB provides some cross-protection against *N. gonorrhoeae*[1]. During a meningococcal outbreak between 2004 and 2006 in New Zealand, MeNZBTM was used, and there was a simultaneous decline in reported cases of gonorrhoea observed during and after its use. Fully vaccinated individuals aged 15–30 years had an adjusted vaccine effectiveness of 31% against *N. gonorrhoeae*[3,23]. The development of the recombinant protein-based 4CMenB (Bexsero®) vaccine is one of the more recent advances in the prevention of invasive meningococcal disease. In a retrospective study in Canada, after a group of individuals from 2 months to 20 years of age were vaccinated in 2014, there was a 59% decline in gonorrhea notifications among people aged 14-20 years was observed during the postvaccination period, suggesting the cross-protection of Bexsero® against *N. gonorrhoeae*[22].

Chlamydia trachomatis

Chlamydia is the most common bacterial STI worldwide[3]. The infections are caused by a range of serovars separated into two major and two minor complexes. Serovars A–C and Ba are major causes of trachoma, D–K, Da, Ia, Ja are linked to genital sexually transmitted diseases and L1–L3 are commonly associated with lymphogranuloma venereum. Vaccine development is ongoing, and the ultimate goal is to design vaccines that cover all of the most prevalent serovars[24].

The prospects for a chlamydia trachomatis (CT) vaccine are increasingly promising, primarily because the last years have seen the rapid development of new tools for Chlamydia research that will accelerate vaccine development. One of the major developments has been the long-awaited technology to genetically manipulate Chlamydia[21]. The major outer membrane protein (MOMP) has been identified as the ideal substitute for whole-cell antigenic targets. The first CT vaccine in clinical development (CTH522/CAF®01) induced neutralizing antibodies directed to the variable domain 4 regions of MOMP, covering predominantly B and intermediate groups of serovars[24]. Although intramuscular immunization has worked effectively for preventing cervical HPV infection, it is unclear whether a CT vaccine can be similarly administered to achieve protection, given the need for robust local T cell immunity. An effective CT vaccine may need to induce strong transmucosal immunity with resident memory T cells in the genital tract[23]. Several new candidate antigens (e.g., polymorphic membrane proteins) are emerging and are showing great promise in both mouse and primate models. It is likely that several candidate vaccines will enter phase I clinical trials in the next few years[21].

Human immunodeficiency virus (HIV)

Globally there were estimated to be 37.9 million PLWH at the end of 2018[23]. In addition, there were 1.7 million new infections with approximately 770,000 AIDS-related deaths in the same year despite the widespread rollout of antiretroviral therapy. The development of potent antiretroviral therapies has transformed HIV infection into a clinically manageable chronic disease. Globally, over 19 million people are now on life-long treatment, and test and treat strategies and oral preexposure prophylaxis (PrEP) could further reduce HIV transmission. However, despite these remarkable advances, prolonged combined antiretroviral therapy (cART) does not eradicate the virus, which often rapidly rebounds upon treatment interruption. In addition, while cART has decreased mortality and morbidity among PLWH, long-term cART treatment is associated with increased occurrence of

Table 1. Vaccines recommendations and dose schedules in the setting of STIs

Vaccine	Recommendations in the context of STIs	Vaccine schedule	References
HAV (Havrix®)	– MSM – Postexposure prophylaxis	Two doses (0 and 6 months-1 year)	28
HBV (Engerix-B®)	– Unvaccinated persons with a high-risk of infection • Multiple sex partners, MSM, HIV+, sex partner of infected person • Postexposure prophylaxis – Anti-Hbs < 10mIU/mL in vaccinated adults • HIV+; sex partners of HBsAg-positive persons	Three doses (0, 1, and 6 months)	2, 29
HPV (Gardasil®9)	– Recommended to all individuals ≤ 26 years-old – Shared clinical decision-making in adults 27-45 years old (e.g. MSM, HIV+, multiple sex partners)	9-14 years old-two doses (0 and 6-12 months) ≥ 15 years old-three doses (0, 2, and 6 months)	2, 29, 30
MPX (Imvanex®)	– MSM, women and transgenders that are on PrEP for HIV and diagnosis of ≥ 1 IST in the last 12 months – MSM living with HIV and diagnosis of ≥ 1 IST in the last 12 months – MSM and transgenders that are sex workers – MSM with severe immunosuppression – Postexposure prophylaxis	2 doses (0, > 28 days) If have been vaccinated against smallpox-one dose	31

a range of serious non-AIDS events. There is a broad scientific consensus that developing a preventive AIDS vaccine that is safe, effective, affordable, and globally accessible is the most effective strategy to control and ultimately eliminate the HIV epidemic. However, despite over three decades of rigorous HIV research and numerous vaccine trials, there is currently no licensed HIV vaccine available on the market[25]. The RV144 trial provided some hope by demonstrating modest but significant vaccine-induced protection (31.2% by 42 months) against HIV acquisition[26]. In the past 30 years, only a few HIV vaccine regimens have been tested in phase 2b clinical trials. Recently, there has been increasing support for adaptive clinical trials aimed at accelerating vaccine development by rapidly evaluating vaccine candidates in small human studies and swiftly advancing promising candidates to efficacy trials. This new accelerated approach has resulted in > 100 HIV vaccine concepts being clinically tested[25].

Herpes simplex virus

Genital herpes is the leading cause of genital ulcers in developed countries. Most cases of recurrent genital herpes are caused by HSV-2; however, an increasing proportion of anogenital herpetic infections have been attributed to HSV-1, which is especially prominent among young women and MSM[2]. HSV is known to establish latency, which makes vaccine development more challenging as an effective vaccine needs to not only prevent active clinical disease but also ideally prevent the virus from entering a latent state. Although there are no currently available vaccines for HSV-1 and 2, there are various candidates in both the preclinical and clinical phases currently in development. The development of the Shingrix® vaccine for herpes zoster and a vaccine for varicella zoster virus has stimulated efforts to develop a vaccine for HSV due to similarities between the two viruses, particularly with regard to their ability to establish latency. Vaccine development efforts are focused on two broad goals—preventative and therapeutic[27]. In recent years, five vaccine candidates have entered phase I/II testing, and several other candidates are currently in development. Most vaccines being tested in clinical trials are aimed at reducing genital herpes recurrences and shedding among individuals who are already infected with HSV-2, known as 'therapeutic vaccination', rather than preventing infection among those who are HSV seronegative[21]. A vaccine that could prevent genital HSV infection and work for both HSV-1 positive and negative individuals, given in adolescence or childhood, would be ideal. The most recent phase III trial for a prophylactic HSV vaccine tested a subunit glycoprotein D2 vaccine on 8,323 North American women who were seronegative for HSV-1 and HSV-2. The trial did not show efficacy against HSV-2 disease, but higher antibody levels of GD-2 were associated with increased efficacy against HSV-1 infection and disease, indicating the first immune correlates of protection against HSV[21,27].

Conclusion

The development of vaccines against STIs is a crucial priority for achieving sustainable global control of these diseases. Currently, effective vaccines are only available for four viral STIs, which include HAV, HBV, HPV and MPX. However, research efforts are ongoing to develop vaccines for other STIs, as they are considered the ultimate solution to the growing epidemic of STIs. The development of HSV vaccines has made significant progress, with multiple promising vaccine candidates in early clinical trials offering hope that an HSV vaccine is on the horizon. However, research on bacterial STIs must also be quickly implemented due to the increased risk of untreatable infections caused by drug resistance. Ensuring vaccine adherence is another important aspect that needs to be emphasized. Healthcare settings, especially those that provide services for STIs, should regularly advise and encourage adults who are at high-risk for STI infection to get vaccinated.

Ethical disclosures

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

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

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

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CASE REPORT

Effect of cannabis use on alopecia areata

Efeito do uso de cannabis na alopecia areata

Abeer AL Lihabi[a]

Department of Psychiatry, College of Medicine, Taibah University, Medina, Saudi Arabia
[a]*ORCID: 0000-0001-7349-6375*

Abstract

Introduction: Alopecia areata (AA) is an autoimmune disease of the hair follicles causing unpredictable hair loss, occurring in about 2% of the general population throughout their lifetime. AA is associated with other concurrent disorders, such as depression, thyroid diseases, and anxiety. Cannabis receptors (CBRs), especially CB2Rs, are found on immune cells, including lymphocytes, macrophages, mast cells, natural killer (NK) cells, peripheral mononuclear cells, and microglia. We report the case of a girl who reported improvement in AA symptoms following marijuana use. **Case presentation**: A 15-year-old girl with alopecia universalis and multiple psychiatric diagnoses started self-medicating with cannabis for her symptoms over a year. She reported hair regrowth on her scalp but not anywhere else on the body. **Conclusion**: Endocannabinoids are a new natural candidate for treating and understanding autoimmunity. There is limited research on the effects of cannabis on AA, and this case report highlights its use as a potential treatment option for autoimmune diseases.

Keywords: Alopecia. Alopecia universalis. Autoimmune disease. Cannabidiol. Cannabis.

Resumo

Introdução: A alopecia areata (AA) é uma doença autoimune dos folículos pilosos que causa queda de cabelo imprevisível, ocorrendo em cerca de 2% da população geral ao longo da vida. A AA está associada a outros distúrbios concomitantes, como depressão, doenças da tireoide e ansiedade. Recetores de cannabis (CBRs), especialmente CB-2Rs, estão presentes em células imunes, incluindo linfócitos, macrófagos, mastócitos, células natural killer, células mononucleares periféricas e micróglia. Relatamos o caso de uma menina que relatou melhoria de AA universal após o uso de marijuana. **A presentação do caso**: Uma menina de 15 anos com alopecia universal e múltiplos diagnósticos psiquiátricos começou a automedicar-se com cannabis para seus sintomas há mais de um ano e relatou crescimento de cabelo no couro cabeludo, mas não em qualquer outro lugar do corpo. **Conclusão**: Os endocanabinóides são um novo candidato natural para o tratamento e compreensão da autoimunidade. Há pesquisas limitadas sobre os efeitos da cannabis na AA, e este relato de caso destaca seu uso como uma potencial opção de tratamento para doenças autoimunes.

Palavras-chave: Alopecia. Alopecia universalis. Doença autoimune. Cannabidiol. Cannabis.

Corresponding author:
Abeer AL Lihabi
E-mail: abulia26@gmail.com

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Background

Alopecia areata (AA) is an autoimmune disease of the hair follicles that causes hair loss in an unpredictable pattern, commonly presenting as a small annular or patchy bald lesion that affects the scalp[1]. A case of total hair loss on the scalp is known as alopecia totalis, and complete hair loss on the entire body is known as alopecia universalis[2]. After hair loss, the regrowth usually takes months and sometimes even several years, but there is never a guarantee for hair growth. However, the best prognostic factor is reported as the extent of hair loss during the index occurrence at the time of diagnosis. A less favorable prognosis is observed in early-onset (during childhood) AA and ophiasis variants. Nevertheless, remission is likely in patients who have had limited patchy hair loss for less than one year[3].

The prevalence of AA is estimated at 2% in the general population (global number) throughout the lifetime. Some studies have indicated that the disease is more prevalent in women, especially those above the age of 45 years. The disease is associated with other concurrent disorders, such as depression, anxiety, and thyroid disease[4]. Concomitant autoimmune diseases frequently occur, such as inflammatory bowel diseases, type 1 diabetes mellitus, and psoriasis, because of shared genes that predispose the individual to these diseases. The autoimmune predisposition is located in the major histocompatibility complex region that encodes the human leukocyte antigen molecules in the human cells, which serves as the major contributor to the AA phenotype of an individual. The immune cluster of differentiation (CD) 4^+, $CD8^+$, T-cell, and NK cells are known as a significant effector of AA disease pathogenesis.

Commonly, the disease onset is associated with a few factors, such as physical or emotional stress, vaccination, and febrile illness. The most frequently used treatment for an acute flare-up includes topical or systemic corticosteroids and, additionally, contact immunotherapy which is considered the most effective treatment for AA[5].

Cannabis is one of the oldest cultivated plants and has been used as raw material, food, and medicinal drug for thousands of years. The renewed interest in cannabis therapies has led to an increase in research on the effective use of cannabis extract, and it has been found that the endocannabinoid system (especially CB2 receptor activation) is a potential target in the treatment of inflammation and autoimmune-related diseases due to the activation of immune cells. CBRs in the brain are present at a high density in the frontal cortex, the basal ganglia, and the cerebellum, besides being in the hypothalamus, hippocampus, and anterior cingulate cortex[6]. Consistently, evidence has demonstrated a possible role for CB1R in the peripheral tissue. On the other hand, CB2Rs are found in immune cells, including lymphocytes, macrophages, mast cells, NK cells, peripheral mononuclear cells, and microglia. The immense articulation of CB2Rs on immune cells is a potential connection between autoimmunity and the use of cannabinoids as a treatment option. A study conducted on a group of high school and university students showed a significant reduction in immunoglobulin M, complement system component (C3, C4) levels in the treatment group that received dried leaves and stems of *Cannabis sativa (C. Sativa)* for about 6-24 months[7]. Additionally, there was a decline in the number of B-lymphocytes and NK cells.

We report the case of a teenage girl suffering from AA resistant to corticosteroids who experienced a marked improvement in hair growth while taking marijuana as an illicit drug.

Case presentation

A 15-year-old girl in 10th grade, diagnosed with mild intellectual disability, suffered from anxiety, particularly around strangers and in crowded places. She reported feeling worried about people judging her and eventually feeling embarrassed when around people. She also experienced bouts of palpitation, tremors, and blushing face and ended up in self-isolation. In her 3rd grade, she was diagnosed with alopecia universals and received multiple corticosteroid trials (intralesional, local, and systemic) with no effects. No other treatment modalities were received. She reported often being bullied and teased at school because of her looks. Consequently, to blend in with her peer group, she got involved in risky adolescent behaviors, such as shoplifting, skipping school, escaping home without parental knowledge, and drug use. She is physically healthy with no medical or other autoimmune disorders.

She began consuming marijuana in the 9th grade, taking it once a week or sometimes twice as well for 6 months. There were no significant side effects except it made her reaction time slow and blurred her judgment. However, smoking partially relieved her anxiety and made her calm. She believed smoking helped her sleep well and overcome the alopecia problem. She reported that gradually her hair started regrowing, especially on the scalp, but the drug had no effect on her eyebrow, lashes, or body hair.

She has difficulty focusing as she gets distracted easily. Due to her forgetfulness and disorganization, she lost essential items. She was reported as short-tempered and resorted to punching walls and windows as a way of expressing her anger. Notably, she has a family history of intellectual disability, attention deficit hyperactivity disorder (ADHD), mood disorders, and anxiety, which serve as significant risk factors. Subsequently, she was diagnosed with ADHD and social anxiety. Since her hair started to grow and reach the right length, she was convinced that cannabis was the most effective remedy for her condition and was unwilling to try any other medication. She was prescribed methylphenidate for ADHD in different forms, which helped her to focus; however, they also resulted in panic attacks and nausea. Her psychoeducational assessment revealed a total score for the first percentile. The appropriate medications were started to treat her anxiety and sleep difficulties, with plans to start a stimulant to treat ADHD symptoms.

Discussion and conclusion

A patient diagnosed with an autoimmune disease often needs a treatment strategy with low or minimal side effects, the most common of which are glucocorticoids, having great potential therapeutic effects. However, there are side effects with prolonged use. On the other hand, endocannabinoid is a new emerging natural candidate for treating and understanding the mechanism underlying autoimmunity. Multiple sclerosis is one of the autoimmune diseases that has reportedly been treated with cannabis[8]. The largest number of randomized controlled trials conducted regarding the medicinal use of cannabis is for the treatment of multiple sclerosis; however, the results of such studies lack consistency, possibly due to different limitations. Such a limitation of the study is it is difficult to completely blind participants to psychoactive substances.

Our patient was using cannabis, which proved to be an effective treatment for her alopecia. After using local and systemic glucocorticoids, she had no response, but after using cannabis, her hair grew, making her feel better about herself as a teen and allowing her to participate in social activities without hiding her hair. Her anxiety has improved to some extent, though we still need to add anxiolytics to her treatment. But the use of cannabis was associated with other risk factors as well. In the long term, she could develop psychosis, depression, or pulmonary disease from cannabis use since she was still young[9]. Attention is drawn to the fact that cannabis as an illicit drug may have medical and psychological consequences and that more medical forms of cannabis are needed to treat such conditions. Smoking cannabis is not the solution, even if it shows good results, since the local form must be examined and tested in these situations. To use cannabis safely in such cases, we need the medical formula and medical guidelines. We should be very careful when reporting such cases not to use cannabis as it is without considering the side effects. It has been reported that daily use of *C. sativa* can increase anxiety levels in a patient or even in a healthy individual[10]. For people aged 17 years and below, daily use of cannabis reduces the chances of a child completing high school, and they are less likely to obtain a college or university degree. Also, driving under the influence of cannabis may cause a risk because it alters the consumer's attention, memory, and decision-making functions. Each person may experience different impairments that may persist after acute intoxication.

On the other hand, the use of cannabis for the treatment of AA is based on the idea of triggering the CB2Rs to suppress the immune response. In a recent cross-sectional survey of 1,087 patients affected by AA, 55% of whom were current marijuana users, the greatest perceived improvement was in the symptoms of stress and psychiatric disorders, such as anxiety, sadness, and depression, while 80.4% of the respondents said the marijuana did not affect their hair loss. However, the study had certain limitations. It was conducted during the coronavirus disease of 2019 pandemic, which may have exacerbated symptoms like loneliness and anxiety. The accuracy of the response rate was uncertain as it was distributed across broad, overlapping listservs. So, further research is needed to elucidate the effects of cannabis on pathological aspects of AA[11].

The present case emphasizes the clinical importance of marijuana in improving AA and the patient's anxiety, thus, boosting her immunity; nevertheless, at the time of the interview, she still had ADHD and anxiety symptoms. In conclusion, endocannabinoids serve as a novel natural candidate for treating and understanding autoimmunity. Since there is a paucity of literature regarding the effects of cannabis on AA, this case report aims to draw attention to the use of endocannabinoids targeting the CB2Rs as a potential treatment option for autoimmune diseases.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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CASE REPORT

Stevens-Johnson syndrome/toxic epidermal necrolysis overlap triggered by ethosuximide: a rare pediatric report

Sobreposicação de síndrome de Stevens-Johnson/necrólise epidérmica tóxica desencadeada por etossuximida: um raro caso pediátrico

Sandra Soares-Cardoso[1,a], Joana Pimenta[1], Flávia Belinha[2], Manuel Salgado[2], Margarida Rato[3], Cristina Pereira[4], and Leonor Ramos[5]*

[1]Department of Pediatrics, Centro Hospitalar Tondela-Viseu, Viseu; [2]Pediatric Intensive Care Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra; [3]Department of Dermatology, Centro Hospitalar Tondela-Viseu, Viseu; [4]Department of Neuropediatrics, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra; [5]Department of Dermatology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[a]ORCID: 0000-0002-0362-5650

Abstract

Introduction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe and life-threatening mucocutaneous conditions characterized by fever and necrosis of the epidermis. Up to 90% of cases are drug-induced. Antiseizure drugs (ASD) are known to cause SJS, but only a very few ethosuximide-induced SJS cases have been reported in the literature. **Case presentation:** We report a case of ethosuximide-induced SJS/TEN overlap in a 4-year-old boy, confirmed by patch tests, with improvement with intravenous immunoglobulin (IVIG) and systemic corticosteroid therapy cycle. **Conclusion:** This case highlights the need to expand knowledge about the optimal treatment strategy for these rare conditions, in addition to supportive treatment.

Keywords: Antiepileptic drug. Ethosuximide. Stevens-Johnson syndrome. Toxic epidermal necrolysis.

Resumo

I**ntroduçao:** A síndrome de Stevens-Johnson (SSJ) e a necrólise epidérmica tóxica (NET) são condições mucocutâneas graves e potencialmente fatais caracterizadas por febre e necrose da epiderme. Até 90% dos casos são induzidos por fármacos. Os antiepiléticos são conhecidos por causar SSJ, mas apenas muito poucos casos de SSJ induzida por etossuximida foram descritos na literatura. **Apresentação do caso:** Relatamos um caso de sobreposição de SSJ/NET desencadeada por etossuximida numa criança de 4 anos, confirmado por testes patch, com melhoria após tratamento com imunoglobulina intravenosa e ciclo de corticoterapia sistémica. **Conclução:** Este caso destaca a necessidade de ampliar o conhecimento sobre a estratégia ideal de tratamento para estas condições raras, além do tratamento de suporte.

Palavras-chave: Antiepiléticos. Etossuximida. Necrólise epidérmica tóxica. Síndrome de Stevens-Johnson.

Corresponding author:
Sandra Soares-Cardoso
E-mail**:** sandraacardosoo@gmail.com

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Introduction

The diseases SJS and TEN are rare but life-threatening mucocutaneous conditions considered a continuum of the same disease[1], characterized by keratinocytes necrolysis, and that are distinguished by the proportion of detached body surface area–SJS involves < 10% of the total body surface area and TEN involves > 30%; between 10 and 30% it is designated as SJS/TEN overlap[2]. These conditions are drug-induced in about 60-90% of cases[2-4]. Children aged 11-15 years and polymedicated patients[2] have the highest incidence. ASD are known to cause SJS[1,5], but only a very few ethosuximide-induced SJS cases have been reported[5-7].

Clinical case

A 4-year-old boy was brought to a level 2 pediatric emergency service with a 2-day history of high fever associated with prostration and anorexia. A total of 18 days before, he was admitted to the pediatric ward due to 7 days of fever associated with a generalized rash (that spared palms and soles), with discharge after clinical improvement with apyrexia.

From personal history to highlight-refractory epilepsy with myoclonic absences, encephalopathy, global development delay, poor stature-weight progression, microcephaly, hypotonia, and ostium secundum atrial septal defect, surgically corrected without a residual shunt. Followed in pediatric neurology consultations at age 2, he was medicated with sodium valproate (40 mg/kg/day), clonazepam (0.05 mg/kg/day), and levetiracetam (40 mg/kg/day); he had started ethosuximide (40 mg/kg/day) 9 days before the onset of the symptoms due to epileptic seizures refractory to ASD. No recent history of immunization was found.

On physical examination, he presented a macular rash (mostly on the face, trunk, limbs, palms, and soles). Laboratory findings showed a white blood cell count of 7.10 x 109/L (55.9% segmented neutrophils and 3.1% eosinophils) and a C-reactive protein of 3.94 mg/dL. Reverse transcriptase polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hemoculture were negative. Serologies for Epstein-Barr virus and *Cytomegalovirus* were compatible with immune status.

He was admitted for surveillance, maintaining a high fever and rash worsening associated with prostration. On the 3rd day of hospitalization (5th day of high fever), he presented with coalescing maculopapular rash that merged on patches and plaques and some atypical target lesions (Figures 1 A-C). Bullous lesions on the flexures, mostly on knees (Fig. 1 D), with positive Nikolsky sign, lip erosions, and edema, with crusted and bleeding lesions (Figures 1 E and F); bilateral eyelid edema (Figures 1 E and F) and oliguria.

The case was discussed with the dermatology and neuropediatrics teams, and due to the suspicion of serious adverse skin reaction associated with ethosuximide, this therapy was discontinued, and he started IVIG (2 g/kg).

Due to the worsening of the general condition with 15% of detached body surface area, he was transferred to a level 3 hospital and initially admitted to the Pediatric Intensive Care Unit (PICU). He remained apyretic and hemodynamically stable. Fulfilled 7 days of parenteral nutrition, with progressive tolerance for enteric feeding. During PICU stay, the treatment approach was under the joint guidance of pediatric dermatology, neuropediatrics, and ophthalmology-daily topical application of fusidic acid and betamethasone and a 3-day course of methylprednisolone (10 mg/kg) followed by a 7-day course of prednisolone (2 mg/kg), with gradual improvement of the rash and oral mucosal lesions. The ocular pseudomembranes were removed every 2 days.

The regular antiepileptic therapy was suspended, only keeping clonazepam at the usual dose without worsening the seizures. He did an electroencephalogram (without sleep and with lots of movement artifacts) with no record of paroxysmal activity.

Serial laboratory evaluations showed no significant changes, and inflammatory parameters remained negative. Serologies for Epstein-Barr virus, *Cytomegalovirus*, herpes simplex virus types 1 and 2, parvovirus B19, *Chlamydia trachomatis*, and *Mycoplasma* pneumonia evidenced previous infection; SARS-CoV-2 and *Bartonella henselae* didn't show active infections. Discharged 34 days after the onset of the illness and only medicated with clonazepam 0.05 mg/kg.

He maintained a multidisciplinary follow-up in the ambulatory consultation, with the resumption of myoclonic absences approximately 2 weeks after discharge (about 10 episodes/day). The dose of clonazepam was duplicated (0.1 mg/kg), and 5 months later, he started a ketogenic diet with significant improvement in seizure control.

Epicutaneous patch tests performed with a reduced Portuguese/European Baseline series, an antiepileptic series, and ethosuximide (a drop of the gel contained in the capsule as is and diluted at 10% in petrolatum) showed a strongly positive reaction (2+) to ethosuximide, whereas no reaction was observed on controls[8]. A skin biopsy was not performed. A genetic study was

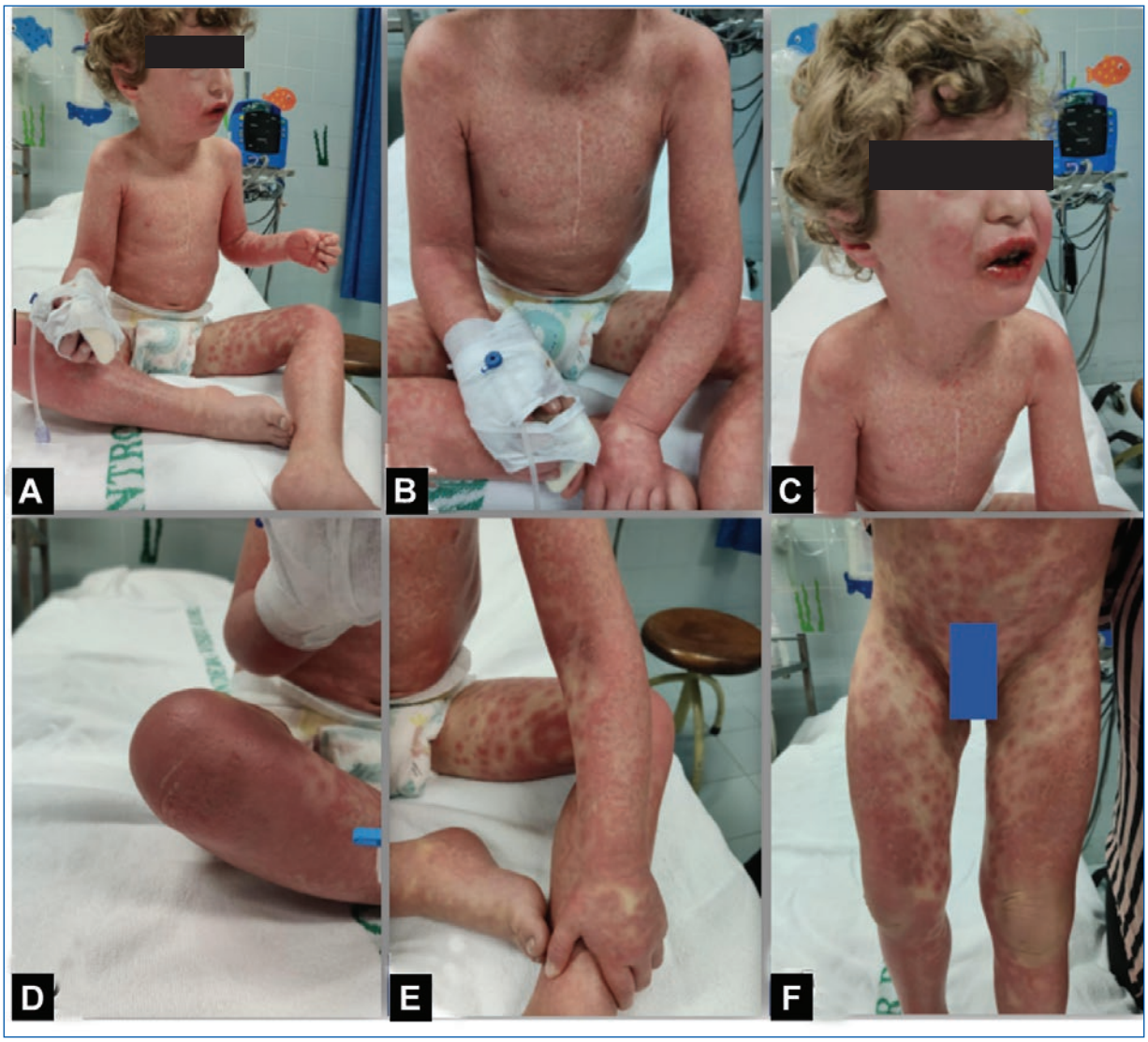

Figure 1. A, B and **C:** clinical presentation on the 5th day of fever with coalescing maculopapular rash, very confluent with target lesions, and **D:** bullous lesions in the flexures, mostly on knees and with **E, F:** bilateral eyelid edema and lip edema with crusted and bleeding lesions.

also carried out, and a variant of uncertain significance was identified in the POLG gene in heterozygosity, probably pathogenic. In order to study the genetic susceptibility for SJS, he's currently awaiting results of the segregation of clinically relevant variants in parents.

Discussion

The diseases SJS/TEN are severe mucocutaneous adverse reactions, and although these conditions are commonly triggered by drugs (risk limited to the first 8 weeks of treatment), they can also have an infectious cause (such as *Mycoplasma* pneumonia, herpes simplex virus, and Epstein-Barr virus) or be caused by immunization, especially in children[4,7].

Diagnostic criteria for SJS/TEN are not consensual, so histologic findings have low specificity. Due to these limitations, the diagnosis of SJS/TEN is based on the following clinical characteristics:

– Suggestive history of exposure to a new drug, 1-3 weeks (average 14 days) before the onset of the symptoms. A new contact with the drug may result in the reappearance of symptoms in < 48 hours-in our case, ethosuximide was started 9 days before the onset of the illness.

- A prodrome of acute-onset febrile illness and malaise-the patient started symptoms 18 days before the hospitalization that led to the diagnosis.
- Painful and rapidly progressive rash described by erythematous macules (coalescing and with the purpuric center), atypical targetoid lesions, or diffuse erythema, all of them developing to vesicles and soft bullae, as shown in Fig. 1.
- Positive Nikolsky and/or Asboe-Hansen signs.
- Oral, ocular, and/or urogenital mucositis with painful and hemorrhagic erosions. In our case, the child presented with cheilitis (Fig. 1C) and ocular pseudomembranes.
- Variable degree of necrosis and epidermis detachment.

Many drugs, including ASD, can cause adverse skin reactions, appearing in approximately 2-3% of prescriptions of a new ASD and being the most common reason for drug discontinuation. Although approximately 95% of adverse skin reactions are mild, such as morbilliform/maculopapular rash or urticaria and/or angioedema, they can occasionally be severe and potentially fatal[6,7]. According to a Japanese study[5] that investigated the characteristics of SJS and TEN associated with ASDs in pediatric patients using a spontaneously reported adverse drug events database, severe cutaneous reactions were associated with multiple ASD. It may be important to avoid polymedication in order to minimize the risk of SJS/TEN during the treatment of children with ASD.

In the literature, there are few reported cases of SJS/TEN associated with ethosuximide, an ASD used mainly to control absence seizures[5-7]. When there is a suspicion of this diagnosis, the identification of the causative drug is essential because its early withdrawal can improve the prognosis[7]. In addition, skin patch tests can be helpful confirming allergy to ethosuximide as it helps to prevent re-exposure in patients recovering from SJS.

The main principles of supportive treatment include wound care, rehydration and electrolyte replacement, nutritional support and temperature, pain, and superinfections control, although prophylactic systemic antibiotics are not recommended. Ocular affection requires urgent care to reduce the risk of permanent ocular sequelae[2].

In addition to supportive care, there are no universally accepted adjuvant therapies for SJS/TEN. Several immunosuppressive or immunomodulatory therapies have been used in clinical practice, including systemic corticosteroids, IVIG, cyclosporine, plasmapheresis, and anti-tumor necrosis factor monoclonal antibodies. None of these therapies have been successfully studied in randomized trials, but there is growing evidence that cyclosporine can slow the progression of SJS/TEN.

The use of systemic corticosteroids remains controversial[9-11]. A large European multicenter study[10] and a meta-analysis[11] suggest that a short course of moderate to high systemic corticosteroid therapy (e.g., prednisone 1-2 mg/kg daily for 3-5 days) may have a beneficial effect if administered within the first 24-48 hours of symptoms. Two pediatric cases described in the literature of SSJ induced by ethosuximide on children at the same age[7] suggested that the therapeutic regimen of corticosteroids and/or IVIG may be effective in treating it, especially in the early stage of illness, as well as the clinical course of our patient.

The diseases SJS/TEN are rare, and the identification of the causative drug is crucial. Its discontinuation should be the first measure to be adopted when the diagnosis is established. In addition to supportive treatment, it's difficult to establish an optimal treatment strategy due to the lack of well-designed clinical trials on outcomes.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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CASE REPORT

Esomeprazole-induced lichen planus

Toxidermia liquenóide associada ao esomeprazol

Miguel Santos-Coelho[a], Joana A. Barbosa[b], Alexandre João[c], and Rodrigo Araújo-Carvalho[d]*

Department of Dermatology and Venereology, Hospital de Santo António dos Capuchos, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal

[a]ORCID: 0000-0002-2288-7306; [b]ORCID: 0000-0001-7351-5302; [c]ORCID: 0000-0002-2517-9604; [d]ORCID: 0000-0002-3228-2482

Abstract

Introduction: Lichenoid drug eruption (LDE) is an uncommon cutaneous drug reaction (CDR) that has classically been associated with anti-hypertensive drugs, gold, and penicillamine. **Case presentation:** We present the case of a 63-year-old woman who developed a pruriginous disseminated dermatosis composed of violaceous polygonal flat-topped papules affecting the flexural aspects of the upper and lower limbs, abdominal flanks, and the lumbar and sacral regions. The lesions started 2 weeks after initiating esomeprazole intake. A histopathological exam of one of the lesions was compatible with LDE. The patient discontinued esomeprazole and was treated with medium potency topical corticosteroids and emollient with full resolution of symptoms. **Conclusion:** Even though CDRs associated with proton-pump inhibitors (PPI) are relatively common, there are only three reported cases of LDE. We report this case to highlight the importance of considering PPIs as the culprit drug in similar clinical situations.

Keywords: Lichenoid drug eruption. Proton-pump inhibitors. Esomeprazole.

Resumo

Introduçao: A toxidermia liquenóide (TL) é uma entidade rara associada, classicamente, ao uso de anti-hipertensores, ouro e penicilamina. **Apresentação do caso:** Apresentamos o caso de uma mulher de 63 anos que desenvolveu uma dermatose disseminada pruriginosa composta por pápulas violáceas poligonais de superfície plana, que afectavam as superfícies flexoras dos membros, flancos e região lombo-sagrada. As lesões surgiram duas semanas após iniciar a toma de esomeprazol. O exame histopatológico de uma lesão foi compatível com o diagnóstico de TL. A doente descontinuou a toma de esomeprazol e foi medicada com um corticóide tópico de média potência e emoliente, com resolução completa dos sintomas. **Concluçao:** Apesar dos efeitos adversos cutâneos serem comuns com a toma de inibidores da bomba de protões (IBP), só existem três casos publicados de TL associada a estes fármacos. Reportamos este caso para destacar a importância de considerar os IBP como agentes causais em situações clínicas semelhantes à descrita.

Palavras-chave: Toxidermia liquenoide. Inibidor da bomba de protões. Esomeprazol.

***Corresponding author:**
Miguel Santos-Coelho
E-mail: mscoelho.derma@gmail.com

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Introduction

Cutaneous drug reactions (CDRs) are a common reason for dermatologic consultation, with a clinical spectrum that ranges from self-limited and benign dermatosis to life-threatening conditions.

LDE has classically been associated with antihypertensive drugs (angiotensin-converting enzyme -inhibitors, β-blockers, and thiazides), gold, and penicillamine[1,2] but over the years, the list of implicated agents has been growing.

A pruriginous rash composed of erythematous scaly papules and plaques usually distributed in the trunk and extremities is the most common presentation. Sometimes, lesions can resemble inflammatory dermatosis like psoriasis or eczema, may follow a photo-distributed pattern[3] and present after a long latent period.

Clinical case

We report the case of a 63-year-old woman with a past medical history of hypertension treated with olmesartan for over 10 years, who developed gastritis and started treatment with esomeprazole 40 mg/day.

Around 2 weeks later, the patient developed a pruriginous disseminated dermatosis composed of violaceous polygonal flat-topped papules affecting the flexural aspects of the upper and lower limbs, abdominal flanks, and the lumbar and sacral regions (Figures 1 A and B). The remaining physical examination was unremarkable. Laboratory workup, including hemogram, ionogram, liver function, and renal function, were normal and anti-hepatitis C virus antibodies, venereal disease research laboratory test, and treponema pallidum haemagglutination test were negative.

A punch biopsy of an abdominal papule revealed irregular epidermal hyperplasia, hypergranulosis, apoptotic keratinocytes, areas of focal parakeratosis, and a dense band-like lymphocytic infiltrate in the upper dermis (Figure 2).

A diagnosis of drug-induced lichen planus (LP) was made. The patient discontinued esomeprazole and was treated with medium-potency topical corticosteroids and emollient twice daily for 1 month. At the 2-month follow-up, most lesions had regressed with postinflammatory hyperpigmentation, and there was no recurrence at 6-month follow-up.

Discussion

Adverse drug reactions frequently involve the skin and follow, in most cases, benign courses. LDEs are relatively uncommon[4] (unlike maculopapular rashes) and usually present in adults (median age 57-66 years)[5].

The pathophysiology of LDE hasn't been fully elucidated, and it is thought to differ, at least partially, from LP. Regardless, $T8^+$ cells and granzyme B appear to be central key factors in its development[1,6].

Differential diagnosis includes LP, subacute lupus erythematosus, psoriasis, eczema, secondary syphilis, and keratosis lichenoid chronica.

Differentiation from LP can be difficult but is crucial, as discontinuation of the inciting drug leads, in most cases, to the resolution of lesions (it is noteworthy, however, that some patients maintain symptoms even after drug removal)[1]. Clinically, classical sites of LP lesions, such as the flexural aspects of the limbs and mucosa, are less commonly affected in LDE and Wickham striae are frequently not found in the latter[1,3]. Histopathologically, even though there are several common features between these two entities, LDE often presents with eosinophils, focal parakeratosis, and focal interruption of the granular layer[6]. In this patient, however, eosinophils were not found on the skin biopsy, which, in itself, does not exclude the diagnosis of LDE.

Time to develop lesions after drug initiation differs between class types and is highly variable, ranging from weeks to several months or even years[1,3].

In this case, clinical and histopathological findings compatible with LDE, temporal association with esomeprazole intake, resolution of symptoms, and lack of recurrence after drug withdrawal favor the diagnosis of esomeprazole-induced LP.

Proton-pump inhibitors (PPI) are one of the most commonly prescribed drug classes, and there are several published reports of cutaneous reactions associated with its use. These range from immediate immunoglobulin E mediated reactions (urticaria and anaphylaxis) to delayed-type hypersensitivity "Stevens-Johnson/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, fixed drug eruption, and drug-induced subacute lupus erythematosus, among others"[4,7]. There are three published case reports of PPI-induced LP[2,4,8]. Two patients were older males (median age 79.5 years)[2,8], one of whom developed LDE to several PPIs[8]. The remaining case was a 2-year-old girl treated with esomeprazole[4]. Resolution of symptoms with drug withdrawal was reported in two of these cases[4,8].

Being a relatively uncommon clinical entity, studies regarding the best clinical approach to treatment are lacking. Drug discontinuation is central to resolution,

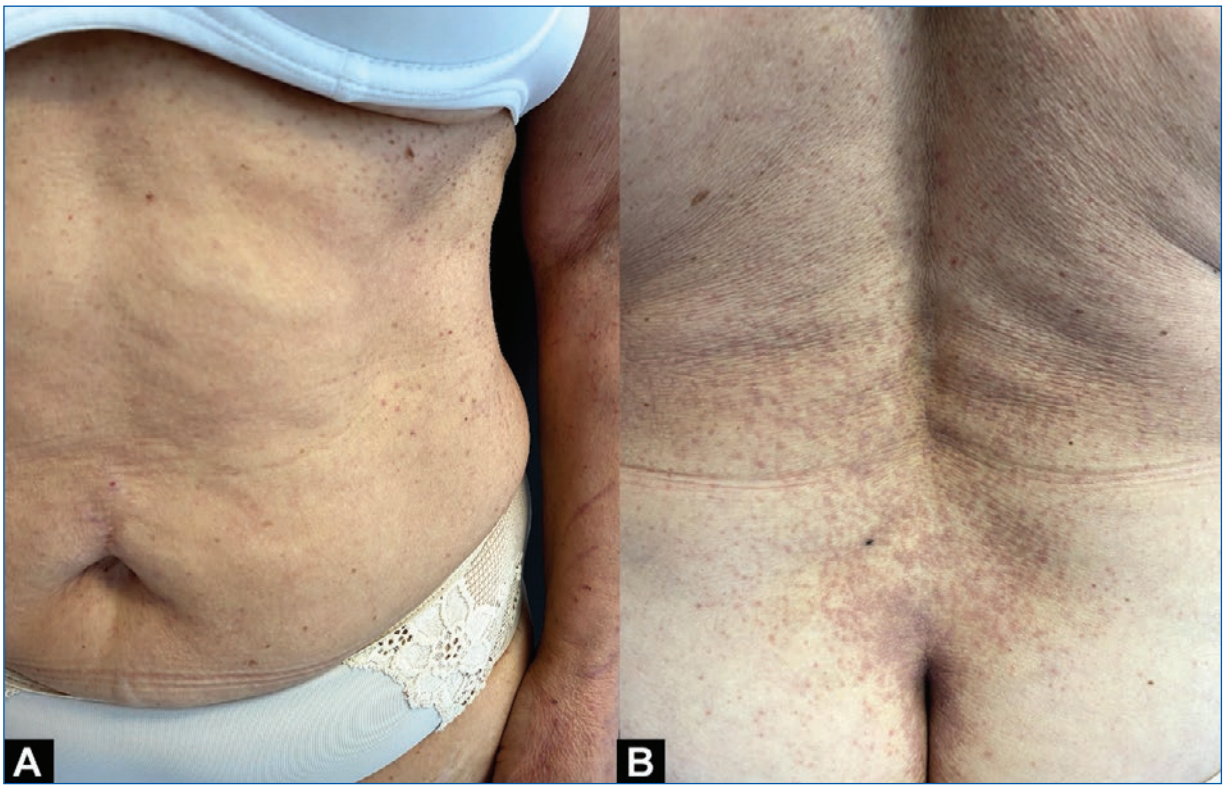

Figure 1. Lichenoid papules affecting the abdominal region **(A)**. Close-up of lumbar and sacral lesions **(B)**.

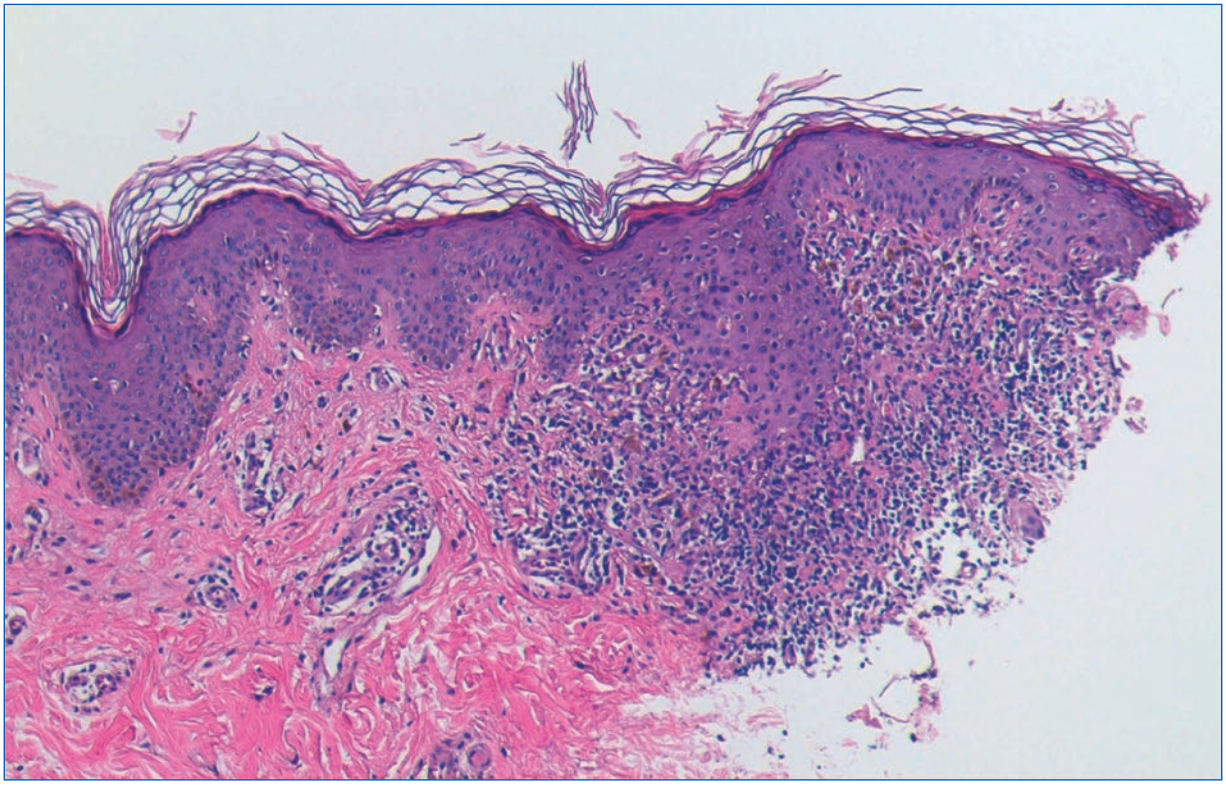

Figure 2. Histopathologic findings of a biopsy of an abdominal papule (hematoxyline-eosin staining, 100×).

and, other than that, topical and systemic corticosteroids are the mainstream treatment[1,2,4].

We report this case to highlight the importance of considering PPI as the culprit drug in similar clinical situations, as PPI-LDE is a rare entity.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

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

Confidentiality of data. The authors declare that 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

Granular cell tumor: rare presentation in pediatric age

Tumor de células granulares: apresentação rara em idade pediátrica

Pedro R. Matos[1,a], Ana Nogueira[1,b], Filomena Azevedo[1,c], and Elisabete Rios[2,d]*

[1]Department of Dermatology and Venereology, Centro Hospitalar e Universitário de São João (CHUSJ); [2]Department of Pathological Anatomy, Centro Hospitalar e Universitário de São João (CHUSJ), Porto, Portugal

[a]ORCID: 0000-0002-4208-7939; [b]ORCID: 0000-0003-4592-3055; [c]ORCID: 0000-0003-0402-6382; [d]ORCID: 0000-0002-3523-5032

Abstract

Granular cell tumors (GCT) are rare soft tissue neoplasms that usually present as solitary lesions, although occasionally, they may be multiple. Most of these tumors arise in the oral mucosa and skin of adults, usually evolving as a slow-growing tumors. It is considered very rare in children. Malignant transformation is very rare, and only 2% of cases are known to spread to distant sites. Here we report a case of a 10-year-old child with a hard painless nodule on the tongue evolving for 6 months. Histopathological examination revealed infiltration of the tongue mucosa by polygonal cells with small nuclei and abundant pale eosinophilic granular cytoplasm expressing S100 protein strongly and diffusely, compatible with a granular cell tumor. A right partial glossectomy was performed. This case highlights the importance of mucosal biopsy for the diagnosis. It also emphasizes that regardless of pediatric age, a biopsy should not be postponed whenever there is uncertainty in the clinical diagnosis.

Keywords: Granular cell tumor. Oral mucosa. Tongue.

Resumo

Os tumores de células granulares são neoplasias raras dos tecidos moles e geralmente surgem como lesões solitárias, embora ocasionalmente sejam múltiplas. A maioria destes tumores ocorre na mucosa oral e na pele de adultos, geralmente evoluindo como um tumor de crescimento lento. Raramente surge em idade pediátrica. A transformação maligna é muito rara, e apenas 2% dos casos podem metastizar para locais distantes. Apresentamos o caso de uma criança de 10 anos com um nódulo duro, indolor, na língua com 6 meses de evolução. O exame histológico revelou infiltração da mucosa lingual por células poligonais exibindo núcleos pequenos e citoplasma granular, eosinofílico pálido, com expressão difusa de S100, compatível com tumor de células granulares. Foi realizada glossectomia parcial direita. Este caso salienta a importância da biópsia de mucosa para o diagnóstico. Ressalta também que, independentemente da idade pediátrica, a biópsia não deve ser adiada sempre que houver incerteza no diagnóstico clínico.

Palavras-chave: Tumor de células granulares. Mucosa oral. Língua.

***Corresponding author:**
Pedro R. Matos
E-mail: pedro.rolo.matos@chsj.min-saude.pt

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Introduction

Granular cell tumors (GCT) are rare soft tissue neoplasms with an incidence estimated in 1:1,000,000 population/year[1,2]. GCT has been reported in patients from all age groups but most commonly appears in the fourth and sixth decades of life[3,4]. Male to female ratio is variable, with some series reporting it more frequently in males while others suggest that it's more common in females[3]. GCT usually appear as solitary lesions, although occasionally, they are multiple and syndromic cases have been reported[5].

Most tumors arise in the oral mucosa and skin, but cases in other organs have been described[1,3,4]. Up to 50% of cases occur in the head and neck region, with lesions arising in the tongue representing one-third of these tumors[4,6]. Classically it is a slow-growing lesion with indefinite borders and a round shape, 5-20 mm in diameter, a whitish color, and a smooth surface, though ulceration may occur in a few cases[4,5]. While local pain is not commonly reported, some discomfort happens during tooth brushing, eating, or oral trauma[7]. The malignant variant is very uncommon, and only 2% of cases have been known to metastasize to distant sites[4,6,8].

Case synopsis

A 10-year-old boy, otherwise healthy, presented to our department due to a hard painless nodule on the tongue. It started as a small swelling that gradually increased in size over the past 6 months.

Physical examination revealed a single whitish nodule, firm, slightly tender on palpation, and about 2 cm in size in the postero-lateral right margin of the tongue (Figure 1).

As the etiology of the lesion was unknown, and it was a relatively large lesion in a child, an incisional biopsy was done. The histology disclosed a mucosa covered by stratified squamous epithelium exhibiting reactive hyperplasia and a poorly circumscribed and infiltrative lesion on the subepithelial tissue composed of polygonal cells with small nuclei and abundant pale eosinophilic granular cytoplasm (Figure 2A to C). The cell borders were indistinct, giving rise to a syncytial appearance. The mitotic index was low, and there was a strong and diffuse expression of S100, highlighting its putative Schwannian origin. Therefore a diagnosis of granular cell tumor was established. The patient underwent a right partial glossectomy, and the surgical margins were tumor free.

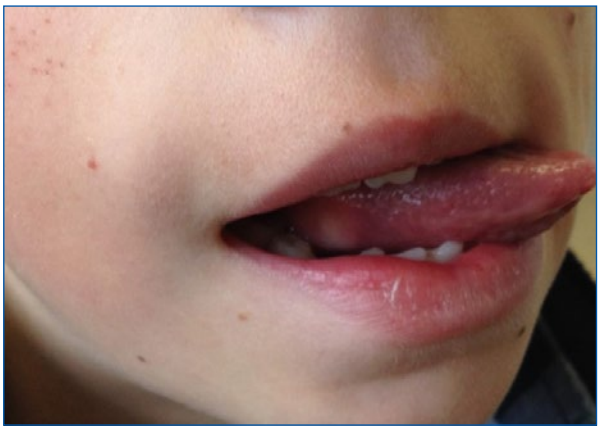


Figure 1. Single whitish nodule, about 2 cm in size in the postero-lateral margin of the tongue.

Discussion

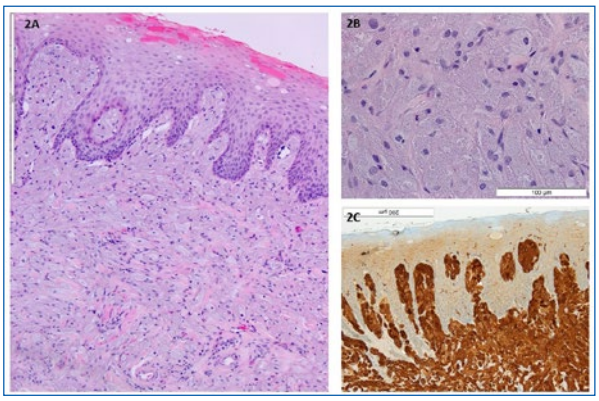
Granular cell tumors (GCT) are rare soft tissue tumors, mostly benign, thought to derive from cells in the nerve sheath[1,9]. S100 protein is the most widely used immunohistochemical marker for these tumors, which was positive in our case[1]. Other immunostains positivity has also been described, such as neuron-specific enolase, cluster of differentiation 68, and calretinin[4,10,11].

Histologically GCT is characterized by non-encapsulated cords, nests, or sheets of infiltrative polygonal and occasionally spindled cells with an abundant granular eosinophilic cytoplasm. Nuclei are small and centrally placed with dense chromatin[4]. An important histological finding reported in up to half of granular cell tumors is pseudoepitheliomatous hyperplasia of the overlying epithelium[1]. Therefore, if the biopsy is too superficial, GCT can be mistaken for a squamous cell carcinoma[12].

As GCT generally occurs in adults in the third to sixth decades and is very rare in the first two decades of life, many other benign lesions have to be considered in the differential diagnosis, including vascular lesions, lipoma, fibroma, or mucous cyst[13].

Furthermore, multiple GCTs have been rarely reported, especially in children with neurofibromatosis, Noonan's syndrome, or growth retardation[14].

Although benign GCTs have an excellent prognosis after local excision, the malignant ones have a poor prognosis, as they are not sensitive to radiotherapy or chemotherapy. Differentiation is based on histological findings, a complete history, physical examination, and other criteria, including size, rapidity of growth, invasion of nearby structures, and the presence of metastasis. Some authors consider it malignant only if it has metastasized[3,8,15].



Figures 2A to C. (A) H&E 100×: mucosa covered by stratified squamous epithelium exhibiting reactive hyperplasia and a poorly circumscribed and infiltrative lesion on the subepithelial tissue, **(B)** H&E 400×: it is composed of polygonal cells with small nuclei and abundant pale eosinophilic granular cytoplasm; pustule-ovoid bodies of Millian corresponding to larger granules surrounded by a clear halo, are also identified, **(C):** strong and diffuse expression of S100 in the neoplastic cells, 200×.

Table 1. Classification of GCTs according to Fanburg-Smith et al. criteria[14]

Criteria	
Increased nuclear-to-cytoplasmic ratio	
Pleomorphism (celular and/or nuclear)	
Tumor necrosis	
Spindling of tumor cells	
Vesicular nuclei with prominent nucleoli	
Mitotic count of > 2 in 10 high-power fields (200× field)	
Classification	
Benign	None of the criteria or focal pleomorphism
Atypical	1-2 criteria
Malignant	≥ 3 criteria

Fanburg-Smith et al. have p roposed six items to consider a granular cell tumor malignant (Table 1)[16]. If three or more of these criteria are present, then the tumor is considered malignant, in which case it grows faster and has the potential to produce metastasis, especially to the regional lymph nodes, liver, lungs, and bone[8].

Regardless of the malignancy, election therapy is the simple conservative excision of the lesion[4]. Relapse occurs more frequently when surgical margins are positive for tumor cells, but some studies have found local relapse even after total excision with free margin[17].

This case is interesting because it is an uncommon tumor that rarely presents at such a young age. In conclusion, regardless of pediatric age, a biopsy should not be postponed whenever there is uncertainty in the clinical diagnosis.

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Conflicts of interest

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

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

A case of unilateral neutrophilic dermatosis of the dorsal hands

Um caso de dermatose neutrofílica do dorso das mãos unilateral

Ana G. Lopes[a], Maria J. Guimarães, Catarina Cerqueira, Cristiana Macedo, Joana Gomes, and Celeste Brito*

Department of Dermatology, Hospital de Braga, Braga, Portugal
[a]ORCID: 0000-0003-1103-1075

Abstract

Our case focuses on a 60-year-old male patient, a farmer, with a previous diagnosis of myelodysplastic syndrome, under regular surveillance at the haemato-oncology department. The patient was referred to the emergency room with an inflammatory ulcerated plaque in the dorsum of his left hand, with 2 weeks evolution. There were two moderately swollen, very painful ulcerated plaques on the dorsal aspect of the left hand, with grayish borders and irregular margins. A skin biopsy showed panniculitis and a dense neutrophilic dermal infiltrate. Attending to his underlying disease, clinical hallmarks of the lesion, and skin biopsy, the diagnosis of a neutrophilic dermatosis of the dorsal hands was made. The patient was treated with oral prednisolone 0.5 mg/kg/day and colchicine 1mg/day with complete regression after 1 month. Neutrophilic dermatosis is a heterogeneous group of skin diseases characterized by dense infiltration of neutrophils in the affected tissue. Neutrophilic dermatosis of dorsal hands is one of them and is considered a localized variant of Sweet syndrome. The etiology is unknown, but about half of the cases are associated with hematological diseases.

Keywords: Myelodysplastic syndrome. Neutrophilic dermatosis. Neutrophilic dermatosis of the dorsal hands. Sweet syndrome.

Resumo

Descreve-se o caso de um doente do sexo masculino de 60 anos, agricultor, com antecedentes pessoais de síndrome mielodisplásico, em vigilância regular em consulta de hemato-oncologia. O doente recorre ao serviço de urgência por placa ulcerada no dorso da mão esquerda, com início duas semanas antes. À observação, eram visíveis 2 placas ulceradas, moderadamente edemaciadas e muito dolorosas na face dorsal da mão esquerda, com bordos acinzentados e margens irregulares. A biópsia cutânea revelou paniculite e um denso infiltrado neutrofílico na derme. Atendendo aos antecedentes do doente, clínica e resultado da biópsia cutânea, foi estabelecido o diagnóstico de dermatose neutrofílica do dorso das mãos. O doente foi tratado com prednisolona oral 0.5 mg/kg/d e colchicina 1mg/d com resolução completa ao fim de 1 mês. As dermatoses neutrofílicas são um grupo heterogéneo de doenças dermatológicas, caracterizadas por um denso infiltrado neutrofílico nos tecidos afetados. A dermatose neutrofílica do dorso das mãos é uma delas, sendo considerada uma variante localizada da síndrome de Sweet. A sua etiologia é desconhecida, mas cerca de metade dos casos estão associados a doenças hematológicas.

Palavras-chave: Síndrome mielodisplásico. Dermatose neutrofílica. Dermatose neutrofílica do dorso das mãos. Síndrome de sweet. Síndrome mielodisplásico.

***Corresponding author:**
Ana G. Lopes
E-mail: anagabri2@gmail.com

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Introduction

Neutrophilic dermatosis of the dorsal hands is a part of the heterogeneous group of neutrophilic dermatoses, considered to be a localized form of Sweet syndrome. It's a rare dermatosis characterized by the sudden appearance of nodules or plaques on the dorsum of the hands, with a dense neutrophilic infiltrate on histology. About half of the cases are associated with hematologic problems.

Here we describe the case of a unilateral neutrophilic dermatosis of the dorsal hands associated with a myelodysplastic syndrome.

Clinical case

Our case focuses on a 60-year-old male patient, a farmer, with a previous diagnosis of myelodysplastic syndrome under regular surveillance at the haemato-oncology department, hemochromatosis, high blood pressure, hyperuricemia, and dyslipidemia.

He had also been previously followed in the Dermatology Department for presenting inflammatory plaques in the limbs 3 years ago. A skin biopsy performed at that time was compatible with leukocytoclastic vasculitis and Sweet syndrome. Lesions resolved with systemic corticotherapy and didn't recur.

The patient presented to the emergency room with an ulcerated lesion on the dorsum of his left hand. This lesion had appeared 2 weeks before as two painful grayish nodules that rapidly proceeded to grow and ulcerate. He denied any history of trauma, itching, recent medication changes, or any other skin lesions.

At dermatological observation, the patient presented two moderately swollen, very painful ulcerated plaques on the dorsal aspect of the left hand with grayish borders and irregular margins (Fig. 1). Blood tests revealed a total leukocyte count of 13.2 x 10^9/L with 51% neutrophils and elevated C-reactive protein of 113 mg/L.

A skin biopsy from the margin of the lesion showed mostly lobular panniculitis, and a dense neutrophilic dermal infiltrate, with no signs of leukocytoclastic or vasculitis. Cutaneous microbiologic cultures yielded negative findings.

Attending to his oncological and dermatological priors, the history and clinical hallmarks of the lesion, and the presence of a neutrophilic infiltrate in the skin biopsy, the diagnosis of a neutrophilic dermatosis of the dorsal hands was made.

The patient was treated with oral prednisolone 40 mg/day (0.5 mg/kg/day), with progressive tapering and colchicine 1 mg/day with quick improvement of the lesion and complete regression after 1 month (Fig. 2). No recurrence has been noted a year after.

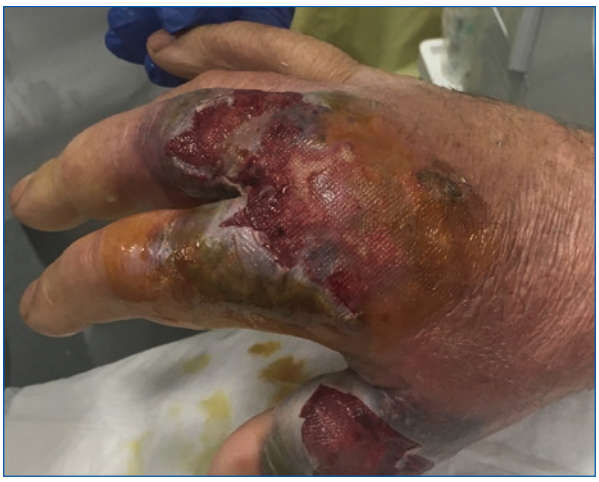

Figure 1. The patient presented to the emergency room with two moderately swollen, very painful ulcerated plaques on the dorsal aspect of the left hand.

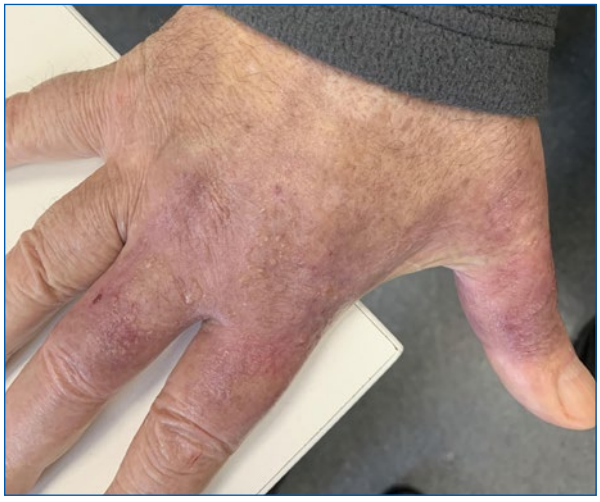

Figure 2. Complete regression of the lesions after 1 month of treatment.

Discussion

Neutrophilic dermatosis is a heterogeneous group of skin diseases characterized by dense infiltration of neutrophils in the affected tissue. Neutrophilic Dermatosis of Dorsal Hands is considered a localized variant of Sweet syndrome since the lesions clinically resemble those of sweet syndrome and show similar histologic evidence of a dense dermal neutrophilic infiltrate. In contrast to Sweet syndrome, however, the distribution is limited almost entirely to the dorsal hands[1].

The etiology is unknown, but about half of the cases are associated with hematologic problems, as in this case, associated with myelodysplastic syndrome. In a review of 123 cases, the underlying disease was found in around 40% of patients, with the most common associations being hematological disorders (gammopathies, myelodysplasias, or malignancies)[2].

Other case reports of this dermatosis were associated with sarcoidosis, hepatitis C, and bowel disorders. Some cases didn't have any localized or systemic triggering factor[3-6].

One unilateral case, as is this one, didn't have any systemic association and occurred at the site of the insect bite, which suggests cutaneous pathergy is associated with this dermatosis[7].

Clinically, this dermatosis presents as painful bluish or gray abscess-like nodules or plaque and blisters on the dorsal aspect of the hands, fingers, or wrists, most frequently in female and elderly patients. Rarely are the palms involved. These lesions may eventually ulcerate in 50% of the cases[8], similar to the case described.

The diagnosis is clinical, but a skin biopsy is often performed for confirmation and will show similar histologic evidence of a dense dermal neutrophilic infiltrate as in Sweet syndrome[9].

The differential diagnoses of this entity include localized cutaneous infection, pyoderma gangrenosum, and other neutrophilic dermatoses[9].

Systemic corticosteroids are the treatment of choice for most cases, and response is usually fast. Given the frequency of relapse, the use of dapsone and colchicine is useful, as they also serve as steroid-sparing agents[10].

Acknowledging the existence of this dermatosis is important since it may be misdiagnosed as a localized cutaneous infection, and a correct diagnosis should trigger a search for underlying diseases.

Funding

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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

Epithelioid angiosarcoma mimicking periorbital cellulitis responsive to paclitaxel

Angiosarcoma epitelióide mimetizando uma celulite periorbital com boa resposta ao paclitaxel

Jessica Baka[a], Ana L. Alves da Silva[b], Felipe Tavares-Rodrigues[c], Daniel Lago-Obadia[d], and Ana L. Sampaio[e]*

Department of Dermatology, Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
[a]ORCID: 0000-0003-2995-2788; [b]ORCID: 0000-0002-4207-3473; [c]ORCID: 0000-0001-9824-6102; [d]ORCID: 0000-0001-9536-1615; [e]ORCID: 0000-0002-5188-1050

Abstract

Introduction and case presentation: We present a rare case of facial angiosarcoma that could be mistaken for cellulitis or lepromatous leprosy. **Conclusion:** The prognosis for the disease is still poor but there are good outcomes descripted with use of drugs such as Paclitaxel.

Keywords: Skin neoplasms. Immunohistochemistry. Differential diagnosis. Treatment outcome. Hemangiosarcoma. Paclitaxel

Resumo

Introduçao e apresentação do caso: Apresentamos um caso raro de angiossarcoma facial que poderia ser confundido com um quadro de celulite ou hanseníase virchowiana. **Concluçao:** O prognóstico para a doença ainda é ruim mas há relatos de bons desfechos com uso de fármacos como o Paclitaxel.

Palavras-chave: Neoplasias cutâneas. Imuno-histoquímica. Diagnóstico diferencial. Resultado do tratamento. Angiossarcoma. Paclitaxel.

Case report

A 72-year-old man with hypertension and Parkinson's disease under oral anticoagulants presented with erythematous papules and periorbital edema on the right hemiface associated with an hyperchromic and pruritic infiltrated plaque in the right frontotemporal region (Fig. 1A), which began two months after a fall and local trauma. Within about one month after the first observation, the lesion progressed with nodule formation, extensive erythematous and violaceous infiltration involving the whole right hemiface and neck, with eyelid edema causing loss of visual capacity (Fig. 1B), but with no associated local or systemic symptoms.

All routine laboratory tests were normal. Differential diagnoses could be Virchowian leprosy with lepromas, facial cellulitis, persistent hematoma and mycosis fungoides. Computed tomography (CT) of the neck did not detect cervical lymphadenopathy. Parotid CT scan did not reveal any atypical findings. Cranial CT revealed

***Corresponding author:**
Felipe Tavares-Rodriguez
E-mail: medftr@yahoo.com.br

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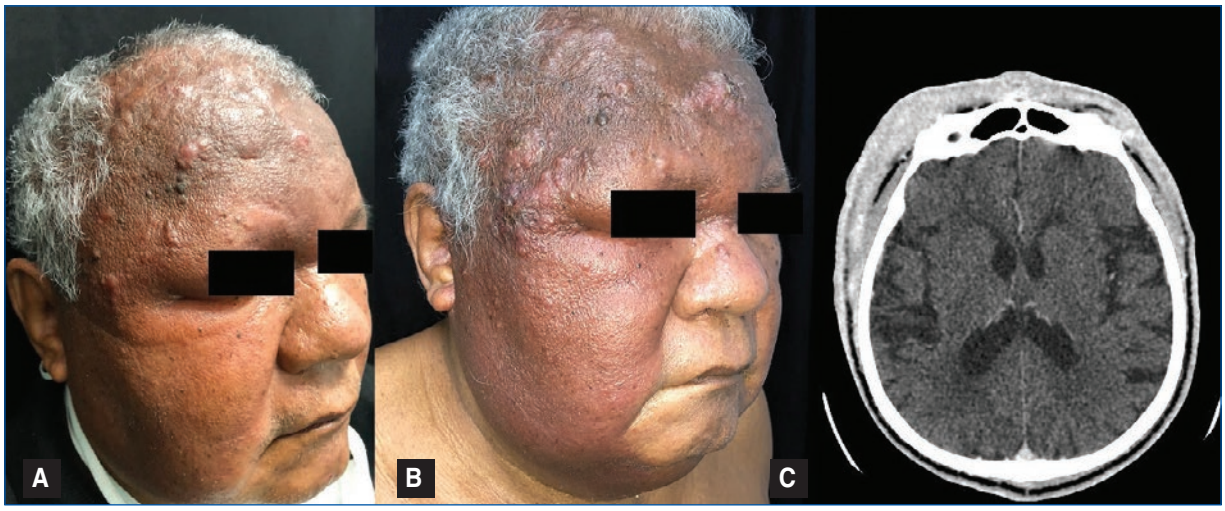

Figure 1. Erythematous-violaceous infiltration on the forehead that evolved to the entire face with the aspect of cellulitis (**A, B**), that on CT showed proliferation of extracranial soft tissues (**C**).

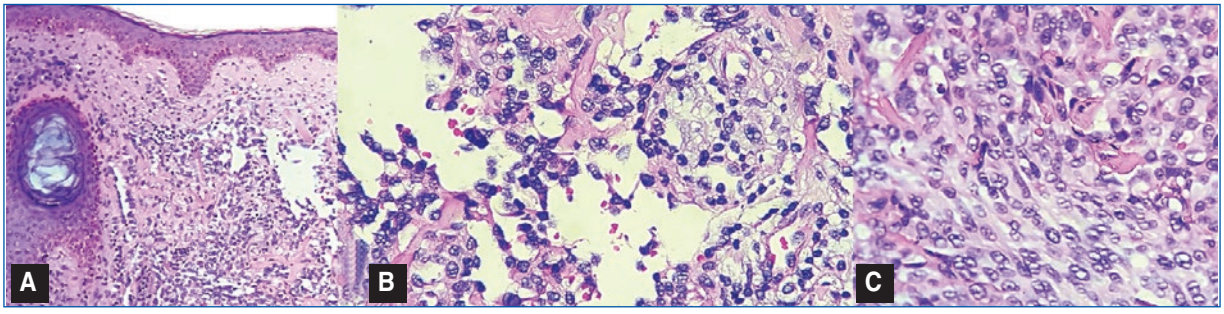

Figure 2. Histopathology showing irregularly shaped anastomosing vascular channels with the presence of atypical endothelial cells infiltrating the dermis (H&E-10x) (**A**) and proliferation of slit-like vessels filled with neoplastic endothelial cells (**B**). Detail of atypical multinuclear endothelial cells (H&E-40x) (**C**).

an increase in soft tissues associated with skin thickening, affecting the frontotemporal and nasoperiorbital regions, especially on the right, with no evidence of collections in the contrast-free study (Fig. 1C).

Histopathology revealed preserved epidermis and diffuse proliferation of atypical epithelioid cells forming masses in the dermis, in addition to vascular channels with bizarre shapes and atypical endothelium (Fig. 1A,B,C). Histopathological differential diagnoses included metastatic carcinoma, sarcoma, melanoma, anaplastic large cell lymphoma, angiosarcoma and other vascular neoplasms. Immunohistochemistry was positive for CD34 (clone QBEnd/10) in multiple vascular channel endothelium and strongly positive for ki67 (clone MIB-1) (Fig. 2A,B) and negative for Cytokeratin Pan (clone AE1AE3), Protein S-100 (clone POLYCLONAL), Carcinoembryonic Antigen–CEA (clone II-7), P63 (clone DAK-P63), and Smooth muscle actin (clone 1A4), therefore confirming the diagnosis of epithelioid angiosarcoma.

Thoracoabdominal and pelvis CT did not identify metastasis. The patient underwent chemotherapy with paclitaxel (175mg/m^2) every 21 days, resulting in a significant improvement in quality of life with return of visual acuity after 2 sessions. After the first cycle, the patient suffered total alopecia and there was a cutaneous bacterial facial infection, with no laboratory alterations, controlled with oral antibiotics. The patient reported nausea and vomiting as the most common adverse event. We have observed a good clinical response after the third cycle of chemotherapy (Fig. 3C). The patient had a significant improvement after completing six chemotherapy cycles and unfortunately died of COVID-19 infection.

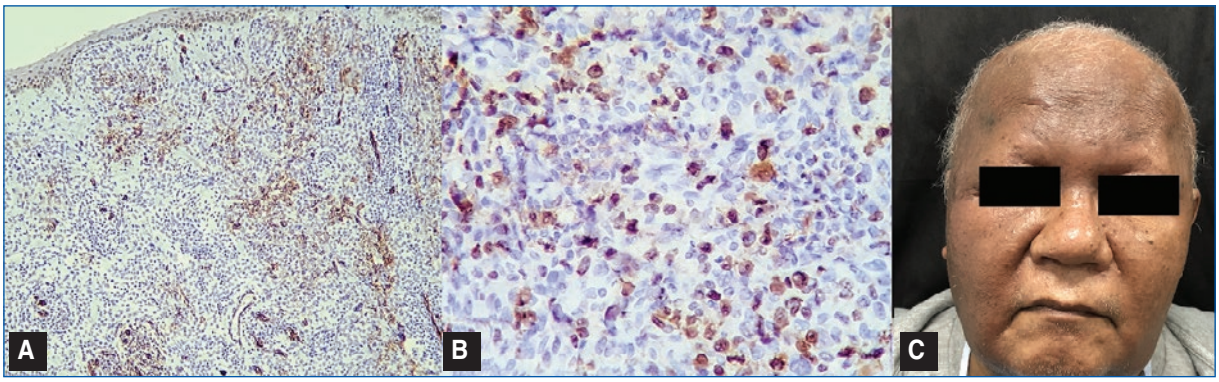

Figure 3. Immunohistochemistry with positive immunostaining positive for CD34 (**A**) and Ki67 (**B**). Clinical improvement after three chemotherapy cycles of paclitaxel (**C**).

Discussion

Epithelioid angiosarcomas are rare and rapidly progressing malignant neoplasms that may clinically resemble hematoma. They may present as erythematous and violaceous nodules, papules, and plaques that can bleed or ulcerate. They typically appear in sun-exposed areas, mainly on the scalp and face, mostly in caucasian men, older than 70 years old. Angiossarcomas can also be associated with chronic lymphedema (Stewart-Treves syndrome) and radiotherapy, particularly in patients undergoing breast cancer treatment[1,2].

Tumor genesis is associated with TP53 tumor suppressor gene suppression and mutations in the PTPRB and PLCG1 genes, which promote angiogenesis. New studies are trying to correlate UV exposition to angiosarcomas development.

The prognosis is poor, with a low five-year survival rate. Generally, patients who have smaller lesions that can be treated with surgical resection and prospective radiotherapy have the best overall survivor rates. However, there are available treatments, with doxorubicin-based regimens and other immunotherapeutic and chemotherapeutic drugs. Furthermore, there are reports of success with paclitaxel, isolated as in the present case, or associated with bevacizumab with or without associated with the use of propranolol[3]. Moreover, propranolol appears as a possible drug to be associated during treatment as it plays a role in stopping tumoral growth. The use of paclitaxel plus propranolol and radiotherapy seems to be one of the best options to treat extensive angiosarcomas nowadays[4,5]. Bevacizumab and other immunotherapeutic drugs appear as a secondary line of treatment and their clinical importance still needs to be evaluated in biggest studies[6].

Funding

None.

Conflicts of interest

None.

Ethical disclosures

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IMAGES IN DERMATOLOGY

Two brownish reticulated patches on the thigh

Duas manchas castanhas reticuladas na coxa

Sofia Antunes-Duarte[1,a], Rita Bouceiro-Mendes[1], and Luís Soares-de-Almeida[1,2]*

[1]Dermatology Department, Hospital de Santa Maria, Centro Hospitalar Universitário; [2]Unit of Research in Dermatology, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

[a]ORCID: 0000-0003-3662-0423

A 41-year-old healthy man presented with a 2-year history of asymptomatic, progressively enlarging lesions on the external aspect of the left thigh. Its onset could not be correlated with trauma, medication or contact with any substance. On examination, two reticulated brownish well-defined patches, with 1 and 1.5 cm in diameter, were observed (Fig. 1A). Biopsy showed a superficial dermal dense, band-like lymphocytic infiltrate accompanied by scattered extravasated erythrocytes (Fig. 2B). A Perls' stain highlighted the hemosiderin deposition (Fig. 2C). It was consistent with lichen aureus (LA).

Lichen aureus is a rare variant of pigmented purpuric dermatoses (PPD), occurring mainly in childhood[1]. Although its etiology remains unknown, its pathogenesis seems to be related to inflammation and hemorrhage of superficial papillary dermal vessels, usually capillaries[2]. It clinically presents with persistent asymptomatic golden to brown colored macules and

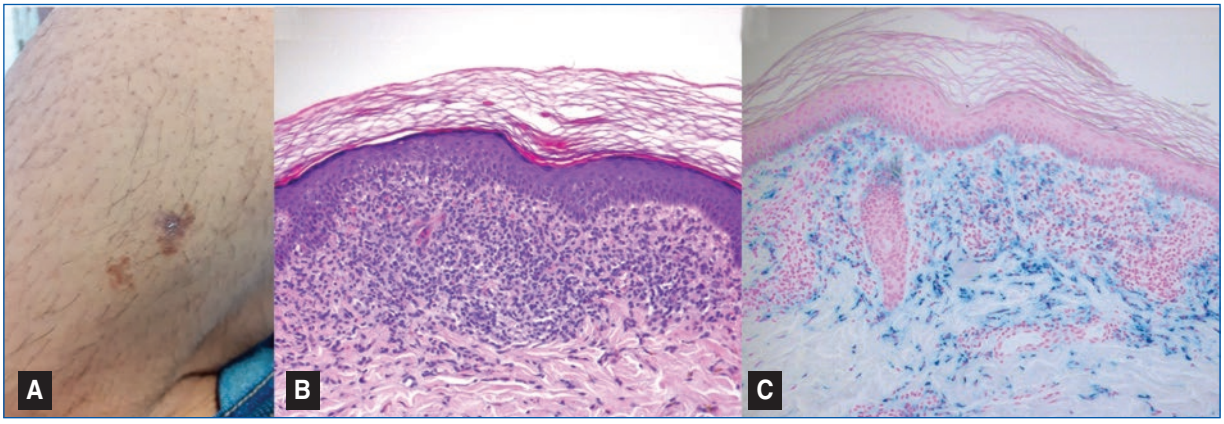

Figure 1. Lichen aureus. **A**: clinical picture of two reticulated brownish patches on the thigh. **B, C**: histopathologic picture revealing a lichenoid infiltrate in the upper dermis with erythrocyte extravasation and hemosiderin deposition evidenced by Perls' stain (B. H&E, x100; C. Perls' stain, x100).

***Corresponding author:**
Sofia Antunes-Duarte
E-mail: sofia.duarte.a@gmail.com

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patches, usually on the lower limbs, with a unilateral distribution[2,3]. Dermoscopy can be useful showing brownish or coppery-red amorphous area, red dots and globules, gray dots and a network of brownish to gray interconnected lines[2,3]. The definitive diagnosis is based on histopathology, with characteristic findings described in the reported case[1-3]. The therapeutic arsenal includes PUVA, calcineurin inhibitors and corticosteroids, frequently with unsatisfactory results[3]. Patients should be reassured regarding the benign and chronic nature of the condition.

Funding

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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IMAGES IN DERMATOLOGY

Hutchinson's sign

Sinal de Hutchinson

Miguel Mansilla-Polo[1,2,a], Miguel A. Navarro-Mira[1,2], and Rafael Botella-Estrada[1,2,3]*

[1]Dermatology Department, La Fe Universitary and Polytechnic Hospital; [2]Health Research Institute (IIS) La Fe; [3]Faculty of Medicine, University of Valencia, Valencia, Spain

[a]ORCID: 0000-0001-6730-6723

A 52-year-old woman with a history of metastatic ovarian cancer under active chemotherapy treatment attended the emergency room due to visual loss and skin lesions of 7 days' evolution.

On examination, a necrotic ulcer was observed that included the nasal tip, the right nasal wing, and the right nasolabial fold. In addition, she presented redness and pain in the ipsilateral eye. The ophthalmological examination revealed corneal opacification with amaurosis of the right eye (Figure 1). Suspecting herpes zoster with ipsilateral nasal and ophthalmic involvement (Hutchinson's sign), a polymerase chain reaction sample of the *Varicella zoster* virus was taken from the ulcer, which confirmed the diagnosis and treatment with intravenous acyclovir at a dose of 10 mg/kg/8 hours for 10 days was performed. Despite the resolution of the skin symptoms, the patient did not recover vision in her right eye.

Hutchinson's sign constitutes involvement of the nasal tip by the *Varicella zoster* virus, often prior to ocular involvement, and anatomically reflects the

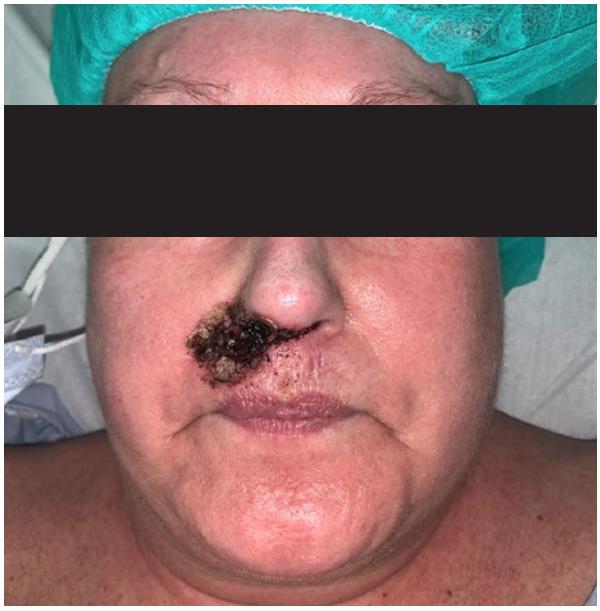

Figure 1. Clinical presentation of the lesions on arrival at the emergency room. Necrotic ulcer located at the tip, right nasal wing, and right nasolabial fold. Corneal redness and opacification in the ipsilateral eye.

***Corresponding author:**
Miguel Mansilla-Polo
E-mail: miguel_yecla96@hotmail.com

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involvement of the nasociliary nerve, which is a branch of the ophthalmic division of the trigeminal nerve.

Early diagnosis and antiviral treatment are essential in these cases since therapeutic withdrawal can lead to irreversible loss of vision[1,2].

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Conflicts of interest

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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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LETTER TO THE EDITOR

Baricitinib as treatment for isolated severe nail lichen planus

Tratamento de líquen plano ungueal grave com baricitinib

Ana L. João[a], Margarida Caldeira, Joana Cabete, Nélia Cunha, and Bruno Duarte*

Department of Dermatology, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal
[a]ORCID: 0000-0002-2489-0138

Dear editor,

Nail involvement occurs in approximately 10% of patients with lichen planus (LP)[1], and isolated nail affection is considered uncommon, although probably overlooked[2]. Nevertheless, nail LP (NLP) may be severe and can rapidly worsen, potentially resulting in irreversible scarring[3]. In addition, treatment is particularly challenging, with high rates of failures and relapses. As a result, NLP may have a significant functional and psychosocial impact[2-4].

We report the case of a 70-year-old female with severe refractory isolated NLP, which had started two decades earlier. All fingernails and toenails were affected (20-nail dystrophy), showing longitudinal ridging and splitting and trachyonychia (Fig. 1A). The diagnosis was confirmed by a nail matrix biopsy. The patient had been previously treated with potent topical, intralesional, and systemic corticosteroids without any significant improvement. She was later treated with methotrexate, with poor response. Baricitinib 2 mg/daily per os was thus initiated, and improvement was noted as early as the 1st month, with considerable recovery of nail changes after 3 months, showing almost complete resolution (Fig. 1B). In addition, the patient also reported significant improvement in finger motricity (due to the reduction of digital pulp pain while grabbing objects). The treatment was well tolerated, without side effects. Given the favorable response, the dosage was not increased, and the patient was kept under close clinical and laboratory follow-up.

Janus kinase (JAK) inhibitors have been revolutionizing the therapeutic armamentarium in dermatology, emerging as promising tools for inflammatory dermatoses[5,6]. In LP, the activation of the interferon-gamma pathway and cluster of differentiation 8 T-cell recruitment is mediated through JAK receptors, explaining the rationale for JAK inhibition in LP[7].

Tofacitinib has been studied in patients with scalp LP[8] and in a patient with NLP[9], with good outcomes. A recent expert consensus has indeed highlighted tofacitinib as a promising therapy for NLP[4]. Baricitinib also proved efficacious in a patient with NLP in a recent report[10].

In sum, NLP is a potentially severe and destructive disease with an unpredictable course and poor long-term prognosis. There is an unmet need for effective therapies for NLP, as no guidelines nor approved drugs are yet available. We present a severe, refractory NLP successfully treated with low-dose baricitinib without side effects in a 70-year-old female, highlighting the promising role of JAK inhibition in this scarring disorder. Additional studies and long-term follow-up are needed to strengthen its role in NLP management.

***Corresponding author:**
Ana L. João
E-mail: luisajoao92@gmail.com

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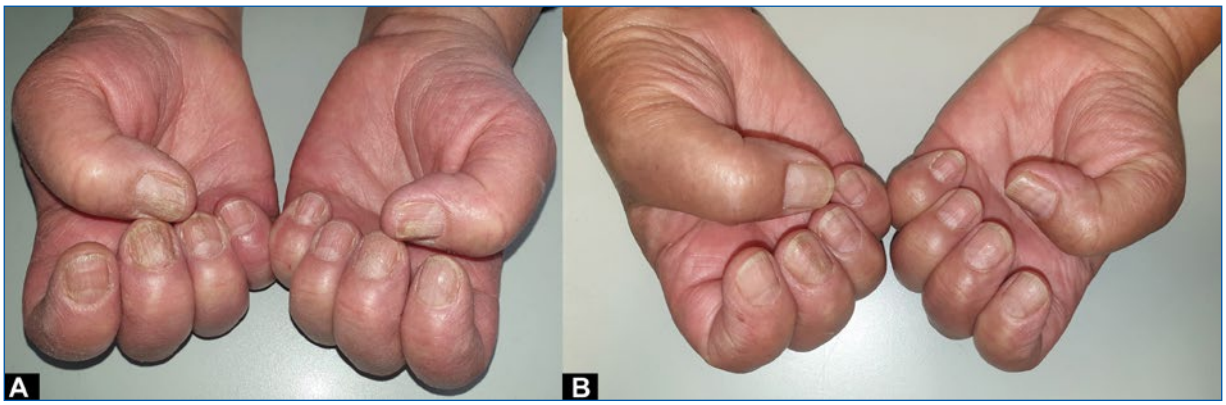

Figure 1. A: longitudinal ridging and splitting, and trachyonychia of all the digits. **B:** significant improvement of the nail changes after 3 months of 2 mg/daily baricitinib, with complete resolution in some digits.

Funding

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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INSTRUCTIONS TO AUTHORS

The Portuguese Journal of Dermatology and Venereol (Port J Derm and Venereol) is the official organ of the Portuguese Society of Dermatology and Venereology, which has been published continuously since 1942, with 4 issues/year. It was formerly known as Revista da Sociedade Portuguesa de Dermatologia e Trabalhos da Sociedade Portuguesa de Dermatologia e Venereologia.

It is an open access, double-blinded, peer-reviewed journal published in English that strives to publish high quality dermatological science with scientific merit and originality as the overriding criteria for publication. It includes review and original articles on basic, clinical, and translational investigation, case reports of special interest, letters to the edi-tor and images cases within the field of Dermatology and Venereology.

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All articles must include without exception:

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– First name, initial of the second name (if applicable) and surname(s) of each author (with-out title or role). Add a hyphen if a second surname is included. Example: Antonio P. Mo-rales; or Antonio Morales, or Antonio P. Morales-Andrade.

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– The institutional departments in which they are assigned: Unit, Service, Department / Hospital / Faculty and University / City, Province, Country

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**Acknowledgements*: All acknowledgements and financing information must be included. This section must go on the front page so that the main document of the manuscript remains anonymous.

2. Full text, tables, and figures

– The texts must be in Word format and correctly written in English.

– The text should be typed in Times New Roman 12. Every new section of the article should start on a new page (abstract in English and keywords; abstract and key words in Portuguese; main text; references + tables + figure captions).

– The pages will be numbered consecutively starting at the front page, and the number will be placed at the top of each page.

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FORMAT OF THE MAIN TEXT

Abstracts

Original articles, including systematic reviews, must contain an abstract in English and one in Portuguese, structured as follows: - Title - Objective - Method – Results - Conclusions – Keywords (maximum 6) with a maximum of 350 words.

Non-structured abstracts should be provided for review articles (maximum 250 words) and case reports (maximum 150 words).

Introduction

It should include the background, and the objective of the study in continuous writing duly supported in the bibliography.

Methods

The characteristics of the sample and the methods used (with relevant references) should be clearly indicated. The statistical methods used should be clearly indicated with the corresponding reference. The authors must include the ethical procedures they have fol-lowed for experiments with animals, patients, management of confidential data, informed consent, etc. and they must confirm having the authorization from the Ethics Committee at their institution.

Results

Results should include relevant findings of the study, comparing them with figures or graphs that are strictly necessary and that extend the information given in the text. In-formation should not be repeated in the text and in the tables and / or figs.

References

References should be presented in Vancouver style and in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Editors of Biomedical Journals). References should be indicated consecutively with Ara-bic numerals, and in the order in which they appear for the first time inside the text and be placed in superscript. The text, tables, and figures (and captions, if applicable) must be referenced as well. In citations with multiple authors (more than six authors), only the first 6 authors of the work should be included, followed by et al., after the abbreviation of the name or names of the 6th author. In the case of 6 or less authors, all of them must be included in the quotation, (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

- Articles published in journals should appear in the following format: Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med. 2004; 351: 987-97.

- References to books must include the full name of the publisher as well as the city and country of publication and the year in which it was published, according to the following model: Aréchiga H, Somolinos J. Mexican contri-butions to modern medicine. Fund of Economic Culture. Mexico D.F., Mexi-co, 1994.

- References to chapters in books should appear as follows: Pasternak RC, Braunwald E. Acute myocardial infarction; or: Harrison's Principles of Inter-nal Medicine. Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (Eds.) McGraw-Hill Inc. 12a. Edition, New York, USA, 1994, pp. 1066-1077.

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Tables must be double-spaced, listed consecutively in the order mentioned in the text, with the titles at the top; the meaning of the abbreviations and explanatory notes should be below. Tables should be included at the end of the manuscript after the references section.

Figures and graphics

– Figure captions should be written in double space. Captions should contain the necessary information to interpret the figure without resorting to the text. They should be refer-enced in the text in order or appearance. Graphics, tracings, and drawings must be sent as high resolution (JPG, TIFF, EPS, PowerPoint and Illustrator). All iconographies must be original. Otherwise, they must be referenced, and the author must obtain prior permis-sion of the respective publisher. Data that has already been written in the text should not be repeated. Photographs of objects should include a rule to calibrate reference meas-urements. Microphotographs should show a microscopic magnification or a reference mi-crometer bar and the staining used.

– The name, face, patient data or any recognizable feature must not appear in the figures.

– Authors are encouraged to add colored illustrations that adequately accompany the text.

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Ethical disclosures

The following form must be submitted when uploading the article on the plat-form: https://www.permanyer.com/formulario-responsabilidades/#

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International Committee of Medical Journal Editors on its web-site http://www.icmje.org. regarding possible conflicts of interest, privacy and confidenti-ality, as well as human and animal rights as subjects of research. A copy of the informed consent will be requested in the case of studies with patients and clinical cases, as well as the approval of the Bioethics Committee of the corresponding institution, in the case of clinical and experimental studies.

The procedures in humans must adhere to the ethical standards of the Helsinki Declara-tion of 1975 (World Medical Association Declaration of Helsinki) Ethical principles for medical research involving human subjects. JAMA 2000; 284: 3043-5, as well as the agreement published by the Ministry of Health on January 26, 1982, and the Rules of the Ethics and Research Committee of the Institution where an original work was carried out. Studies in animals should follow similar guidelines (Institute of Laboratory Animal Re-sources, National Research Council, Guide for the care and use of laboratory animals, Washington, DC, National Academy Press, 1996). In relation to data confidentiality data, the way in which the anonymity of the participants and the privacy of their information have been protected must be informed.

Funding

The author should mention the organizations that fund, including grants or similar, if ap-plicable.

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Authors should describe any financial or personal relationship they have with other peo-ple or organizations that could lead to a conflict of interest in relation to the article sub-mitted for publication.

TYPES OF ARTICLES

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Editorials are normally written at the invitation of the Editor and consist of commentary on articles published in the journal or on subjects of particular relevance. Editorials should not exceed 1200 words and 10 references and may include 1 table and 1 figure. Abstract is not required.

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The maximum extension should be 4000 words and up to 50 references. It presents the results of original clinical investigation or basic research. In the original articles the body of the manuscript should be structured by: Introduction, Methods, Results, Discussion and Conclusions, Figures and Tables.

In the case of clinical trials they should follow the CONSORT Statement (http://www.consort-statement.org/) and should be registered in a public trials registry in accordance with International Committee of Medical Journal Editors (IC-MJE, http://www.icmje.org) recommendations. The clinical trial registration number should be included at the end of the abstract of the article.

Systematic reviews

Systematic Reviews can be presented in the Introduction, Methods, Results, Discussion format. The subject must be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis. We strongly encourage authors to comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/).

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Case Reports should include the following sections: Introduction, Clinical Case, and Dis-cussion. Clinical case studies should not exceed 1500 words and 15 references.

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This is a section for showing images of interest in Dermatology and Venerology. It may involve clinical, histological or image aspects, or any other that is considered relevant for dermatologists. A maximum of three illustrations of excellent quality should be sent, ac-companied by a brief description that highlights the importance of the image (250 words max) and up to 5 bibliographical references can be included. Patients' privacy must be strictly maintained.

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They are meant to expose: 1) positive or negative comments in response to a previous publication, or:

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Requirements	Editorial	Original articles	Review Articles	Case reports	Dermatology images	Letters to the Editor
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3. Abstract + Keywords (Portuguese)	-	Yes	Yes*	Yes*	-	-
4. Content (max words)	Yes (1200)	Yes (4000)	Yes (5000)	Yes (1500)	Yes (250)	Yes (800)
5. Bibliography (Max references)	Yes (10)	Yes (50)	Yes (100)	Yes (15)	Yes (5)	Yes (10)
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Referências: 1. RCM - Resumo das características do medicamento. **2.** Gandhi NA et al. Nat Rev Drug Discov 2016; 15:35–500. **3.** Blauvelt A et al. Lancet 2017; 389:2287–2303. **4.** Silverberg JI et al. Acta Derm Venereol 2021; 101(11):adv00585. **5.** Simpson EL et al. JAMA Dermatol 2020; 156(1):44–56. **6.** Data on file (AD-1652 CSR CDLQI rate). Sanofi and Regeneron Pharmaceuticals, Inc. 2019. **7.** Paller AS et al. Am J Clin Dermatol 2020; 21:119–131. **8.** Paller AS et al. J Am Acad Dermatol 2020; 83(5):1282–1293. **9.** Cork MJ et al. Poster presented at the Revolutionizing Atopic Dermatitis Conference; 2021; June 13; Virtual Conference. Poster 468. **10.** Blauvelt A et al. Poster presented at the Revolutionizing Atopic Dermatitis Conference; 2021; June 13; Virtual Conference. Poster 469. **11.** IQVIA Sanofi Integrated DUPIXENT Platform, data through October 2021. **12.** Bagel J et al. Poster presented at the 30th Congress of the European Academy of Dermatology and Venereology; 2021; September 29–October 2; Virtual Meeting. Poster P0257. **13.** de Wijs LEM et al. Br J Dermatol. 2021; 185(3):555–562. **14.** de Wijs LEM et al. Br J Dermatol 2020; 182(2):418–426. **15.** Fargnoli MC et al. J Dermatolog Treat 2021; 32(5):507–513. **16.** Ariëns LF et al. Allergy 2020; 75(1):116–126.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO Nome do medicamento Dupixent 300 mg solução injetável em seringa pré-cheia Dupixent 300 mg solução injetável em caneta pré-cheia Dupixent 200 mg solução injetável em seringa pré-cheia Dupixent 200 mg solução injetável em caneta pré-cheia **Composição Qualitativa e Quantitativa** Dupixent 300 mg solução injetável em seringa pré-cheia ou caneta pré-cheia Cada seringa pré-cheia ou caneta pré-cheia de utilização única contém 300 mg de dupilumab em 2 ml de solução (150 mg/ml). Dupilumab 200 mg solução injetável em seringa pré-cheia ou caneta pré-cheia Cada seringa pré-cheia de utilização única contém 200 mg de dupilumab em 1,14 ml de solução (175 mg/ml). Dupilumab é um anticorpo monoclonal totalmente humano, produzido em células de ovário de hamster chinês (CHO) por tecnologia de ADN recombinante. Lista completa de excipientes, ver secção 6.1. do RCM completo. **Forma Farmacêutica** Solução injetável (injetável) Solução estéril transparente a ligeiramente opalescente, incolor a amarelo pálido, isenta de partículas visíveis, com um pH aproximado de 5,9. **Indicações terapêuticas** Dupixent 200 mg e 300 mg: Dermatite atópica *Adultos e adolescentes* Dupixent é indicado para o tratamento de dermatite atópica moderada a grave em adultos e adolescentes com idade igual ou superior a 12 anos que são candidatos a terapêutica sistémica. *Crianças dos 6 meses aos 11 anos de idade* Dupixent é indicado para o tratamento de dermatite atópica grave em crianças dos 6 meses aos 11 anos de idade que são candidatos a terapêutica sistémica. Asma *Adultos e adolescentes* Dupixent é indicado em adultos e adolescentes com idade igual ou superior a 12 anos como tratamento complementar de manutenção para asma grave com inflamação tipo 2 caraterizada por eosinófilos elevados no sangue e/ou fração exalada de óxido nítrico (FeNO) aumentada, ver secção 5.1. do RCM completo, que são inadequadamente controlados apesar das doses elevadas de corticosteroides inalados (ICS) associados a outro medicamento para tratamento de manutenção. Crianças dos 6 aos 11 anos de idade Dupixent é indicado em crianças dos 6 aos 11 anos de idade como tratamento complementar de manutenção para asma grave com inflamação tipo 2 caracterizada por eosinófilos elevados no sangue e/ou fração exalada de óxido nítrico (FeNO) aumentada, ver secção 5.1, que são inadequadamente controlados com doses médias a elevadas de corticosteróides inalados (ICS) associados a outro medicamento para tratamento de manutenção. Dupixent 300 mg: Rinossinusite crónica com polipose nasal (CRSwNP) Dupixent é indicado como terapia complementar com corticosteróides intranasais para o tratamento de adultos com CRSwNP grave, para quem a terapia com corticosteróides sistémicos e/ou cirurgia não fornece controlo adequado da doença. Dupixent 300 mg: Prurigo Nodular (PN) Dupixent é indicado para o tratamento de adultos com prurigo nodular (PN) moderado a grave que são candidatos a terapêutica sistémica. Dupixent 300 mg: Esofagite Eosinofílica (EoE) Dupixent é indicado para o tratamento da esofagite eosinofílica em adultos e adolescentes com idade igual ou superior a 40 kg, inadequadamente controlados, intolerantes ou não candidatos à terapêutica medicamentosa convencional (ver secção 5.1 do RCM completo). **Posologia e modo de administração** O tratamento deve ser iniciado por profissionais de saúde com experiência no diagnóstico e tratamento de condições para os quais o dupilumab está indicado (ver secção 4.1 do RCM completo). **Posologia** Dermatite atópica *Adultos* A dose recomendada de dupilumab para doentes adultos é uma dose inicial de 600 mg (duas injeções de 300 mg), seguida de 300 mg administrados em semanas alternadas sob a forma de injeção subcutânea. *Adolescentes (12 aos 17 anos de idade)* A dose recomendada de dupilumab para doentes adolescentes dos 12 aos 17 anos de idade está especificada na Tabela **1. Tabela 1: Dose de dupilumab para administração subcutânea em doentes adolescentes dos 12 aos 17 anos de idade com dermatite atópica Peso corporal do doente** menos de 60 kg **Dose inicial** 400 mg (duas injeções de 200 mg) **Doses subsequentes (em semanas alternadas)** 200 mg; **Peso corporal do doente** 60 kg ou mais **Dose inicial** 600 mg (duas injeções de 300 mg) **Doses subsequentes (em semanas alternadas)** 300 mg. *Crianças dos 6 aos 11 anos de idade* A dose recomendada de dupilumab para crianças dos 6 aos 11 anos de idade está especificada na Tabela 2. **Tabela 2: Dose de dupilumab para administração subcutânea em crianças dos 6 aos 11 anos de idade com dermatite atópica Peso corporal do doente** de 15 kg a menos de 60 kg **Dose inicial** 300 mg (uma injeção de 300 mg) no Dia 1, seguida de 300 mg no Dia 15 **Doses subsequentes** 300 mg a cada 4 semanas (Q4W)* começando 4 semanas após a dose do Dia 15; **Peso corporal do doente** 60 kg ou mais **Dose inicial** 600 mg (duas injeções de 300 mg) **Doses subsequentes** 300 mg em semanas alternadas (Q2W). *a dose pode ser aumentada para 200 mg Q2W em doentes com peso corporal de 15 kg a menos de 60 kg com base na avaliação do médico. *Crianças dos 6 meses aos 5 anos de idade* A dose recomendada de dupilumab para crianças dos 6 meses aos 5 anos de idade está especificada na Tabela **3. Tabela 3: Dose de dupilumab para administração subcutânea em crianças dos 6 meses aos 5 anos de idade com dermatite atópica Peso corporal do doente** de 5 kg a menos de 15 kg **Dose inicial** 200 mg (uma injeção de 200 mg) **Doses subsequentes** 200 mg a cada 4 semanas (Q4W); **Peso corporal do doente** de 15 kg a menos de 30 kg **Dose inicial** 300 mg (uma injeção de 300 mg) **Doses subsequentes** 300 mg a cada 4 semanas (Q4W). Dupilumab pode ser utilizado com ou sem corticosteroides tópicos. Poderão ser utilizados inibidores da calcineurina tópicos, mas devem ser reservados apenas para as áreas problemáticas, tais como a face, o pescoço e as áreas intertriginosas e genitais. Deve ter-se em consideração a interrupção do tratamento em doentes que não tenham apresentado resposta após 16 semanas de tratamento para a dermatite atópica. Alguns doentes com resposta parcial inicial podem subsequentemente melhorar com a continuação do tratamento além das 16 semanas. Se for necessária a interrupção do tratamento com dupilumab, os doentes podem ser tratados novamente com sucesso. Asma *Adultos e adolescentes* A dose recomendada de dupilumab para adultos e adolescentes (idade igual ou superior a 12 anos) é: • Em doentes com asma grave e terapêutica oral com corticosteróides ou doentes com asma grave e dermatite atópica comórbida de moderada a grave ou em adultos com rinossinusite crónica com polipose nasal comórbida grave, uma dose inicial de 600 mg (duas injecções de 300 mg), seguida de 300 mg administradas em semanas alternadas sob a forma de injecção subcutânea • Para todos os outros doentes, uma dose inicial de 400 mg (duas injecções de 200 mg), seguida de 200 mg administradas em semanas alternadas sob a forma de injecção subcutânea. *Crianças dos 6 aos 11 anos de idade* A dose recomendada de dupilumab para doentes pediátricos dos 6 aos 11 anos de idade está especificada na Tabela 4. **Tabela 4: Dose de dupilumab para administração subcutânea em crianças dos 6 aos 11 anos com asma Peso corporal do doente** de 15 kg a menos de 30 kg **Dose inicial ou Doses subsequentes** 100 mg em semanas alternadas (Q2W) ou 300 mg a cada quatro semanas (Q4W); **Peso corporal do doente** de 30 kg a menos de 60 kg **Dose inicial ou Doses subsequentes** 200 mg em semanas alternadas (Q2W) ou 300 mg a cada quatro semanas (Q4W); **Peso corporal do doente** 60 kg ou mais **Dose inicial ou Doses subsequentes** 200 mg em semanas alternadas (Q2W). Para doentes pediátricos (dos 6 aos 11 anos) com asma e dermatite atópica grave co-mórbida, conforme indicação aprovada, a dose recomendada deve ser seguida na Tabela 2. Os doentes tratados concomitantemente com corticosteróides orais, podem reduzir a sua dose de esteróides, uma vez que tenha ocorrido uma melhoria clínica com o dupilumab (ver secção 5.1 do RCM completo). A redução dos esteróides deve ser realizada gradualmente (ver secção 4.4 do RCM completo). Dupilumab destina-se a tratamento de longo prazo. Deve ser considerada a necessidade de terapia continuada pelo menos numa base anual, conforme determinado pela avaliação médica do nível de controlo da asma do doente. Dupixent 300 mg: Rinossinusite crónica com polipose nasal (CRSwNP) A dose recomendada de dupilumab para doentes adultos é uma dose inicial de 300 mg seguida de 300 mg administradas em semanas alternadas. O dupilumab destina-se a tratamento de longo prazo. Deve ser considerada a interrupção do tratamento em doentes que não apresentem resposta após 24 semanas de tratamento para a CRSwNP. Alguns doentes com resposta parcial inicial podem melhorar posteriormente com o tratamento continuado além das 24 semanas. Dupixent 300 mg: Prurigo Nodular (PN) A dose recomendada de dupilumab para doentes adultos é uma dose inicial de 600 mg (duas injeções de 300 mg), seguida de 300 mg administradas em semanas alternadas. Dupilumab pode ser utilizado com ou sem corticosteróides tópicos. Estão disponíveis dados de ensaios clínicos para o PN em doentes tratados até 24 semanas. Deve ser considerada a interrupção do tratamento em doentes que não tenham demonstrado resposta após 24 semanas de tratamento para o PN. Dupixent 300 mg: Esofagite Eosinofílica (EoE) A dose recomendada de dupilumab para doentes com idade igual ou superior a 12 anos é de 300 mg administrados semanalmente (QW). Dupilumab 300 mg QW não foi estudado em doentes com EoE com peso inferior a 40 kg. Dupilumab destina-se a tratamento a longo prazo. Dupilumab 300 mg QW foi estudado até 52 semanas. A dosagem para além das 52 semanas não foi estudada. Dose esquecida Se uma dose semanal for esquecida, administre a dose o mais rápido possível, iniciando um novo esquema com base nesta data. Se uma dose em semanas alternadas for esquecida, administrar a injeção no prazo de 7 dias a partir da dose esquecida e depois retomar o esquema habitual do doente. Se a dose esquecida não for administrada no prazo de 7 dias, aguardar até a dose seguinte no esquema habitual. Se uma dose a cada 4 semanas for esquecida, administrar a injeção no prazo de 7 dias a partir da dose esquecida e depois retomar o esquema habitual do doente. Se a dose esquecida não for administrada no prazo de 7 dias, administrar a dose, iniciando um novo esquema com base nesta data. Populações especiais *Idosos (≥65 anos)* Não é recomendado qualquer ajuste posológico para os doentes idosos (ver secção 5.2 do RCM completo). *Compromisso renal* Não é necessário qualquer ajuste posológico nos doentes com insuficiência renal ligeira ou moderada. Estão disponíveis dados muito limitados sobre doentes com insuficiência renal grave (ver secção 5.2 do RCM completo). *Compromisso hepático* Não estão disponíveis dados sobre doentes com insuficiência hepática (ver secção 5.2 do RCM completo). *Peso corporal* Dupixent 200 mg: Não é recomendado qualquer ajuste posológico para o peso corporal em doentes com asma com idade igual ou superior a 12 anos ou em adultos com dermatite atópica (ver secção 5.2 do RCM completo). Dupixent 300 mg: Não é recomendado qualquer ajuste posológico para o peso corporal em doentes com asma e EoE com idade igual ou superior a 12 anos ou em adultos com dermatite atópica ou CRSwNP, ou PN (ver secção 5.2 do RCM completo). População pediátrica A segurança e eficácia de dupilumab em crianças com dermatite atópica com menos de 6 meses de idade não foram estabelecidas. A segurança e eficácia de dupilumab em crianças com peso corporal < 15 kg não foram estabelecidas. Não existem dados disponíveis. A segurança e eficácia de dupilumab em crianças com asma grave com menos de 6 anos de idade não foram estabelecidas. Não existem dados disponíveis. Dupixent 300 mg: A segurança e eficácia em crianças com CRSwNP com idade inferior a 18 anos não foram estabelecidas. Não existem dados disponíveis. Dupixent 300 mg: A segurança e eficácia do dupilumab em crianças com PN abaixo dos 18 anos de idade não foram estabelecidas. Não existem dados disponíveis. Dupixent 300 mg: A segurança e eficácia de dupilumab em crianças com EoE abaixo dos 12 anos não foram estabelecidas. **Modo de administração** Via subcutânea A caneta pré-cheia de dupilumab não se destina a ser utilizada em crianças com menos de 12 anos de idade. Para crianças dos 6 meses aos 11 anos de idade com dermatite atópica e asma, a seringa pré-cheia de dupilumab é a apresentação apropriada para administração a essa população. Dupilumab é administrado por injeção subcutânea na coxa ou no abdómen, excetuando na área de 5 cm à volta do umbigo. Se for outra pessoa a administrar a injeção, também pode ser utilizada a região superior do braço. Cada seringa pré-cheia ou caneta pré-cheia é apenas para utilização única. Dupixent 200 mg: Para a dose inicial de 400 mg, administrar duas injeções de 200 mg consecutivamente em locais de injeção diferentes Dupixent 300 mg: Para a dose inicial de 600 mg, administrar duas injeções de 300 mg de Dupixent consecutivamente em locais de injeção diferentes. Recomenda-se que vá alternando o local de injeção. Dupilumab não deve ser injetado em pele sensível ao toque, lesionada ou que tenha equimoses ou cicatrizes. Os doentes podem autoinjetar dupilumab ou o prestador de cuidados do doente pode administrar dupilumab, caso o seu profissional de saúde determine que tal é apropriado. Deve ser proporcionada formação adequada aos doentes e/ou aos prestadores de cuidados sobre a preparação e a administração de dupilumab antes de utilizar de acordo com a secção Instruções de utilização no final do folheto informativo. **Contraindicações** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1 do RCM completo. **Efeitos indesejáveis** *Resumo do perfil de segurança* As reações adversas mais frequentes na dermatite atópica, asma e CRSwNP são reações no local de injeção (incluindo eritema, edema, prurido, dor e inchaço), conjuntivite, conjuntivite alérgica, artralgia, herpes oral, e eosinofilia. Uma reação adversa adicional de equimose no local de injeção foi notificada em EoE. Foram notificados casos raros de reações de doença do soro, reações do tipo doença do soro, reação anafilática, e queratite ulcerosa (ver secção 4.4 do RCM completo). *Lista tabelada de reações adversas* Os dados de segurança do dupilumab apresentados na Tabela 5 foram obtidos principalmente a partir de 12 ensaios clínicos aleatorizados e controlados por placebo, incluindo dermatite atópica, asma e doentes com CRSwNP. Estes estudos envolveram 4.206 doentes que receberam dupilumab e 2.326 doentes que receberam placebo durante o período controlado e são representativos do perfil geral de segurança do dupilumab. Listadas na Tabela 5 estão as reações adversas observadas em estudos clínicos e/ou após o início da comercialização, apresentadas por classe de sistema de órgãos e frequência, utilizando as seguintes categorias: muito frequentes (≥ 1/10); frequentes (≥ 1/100, < 1/10); pouco frequentes (≥ 1/1.000, < 1/100); raras (≥ 1/10.000, < 1/1.000); muito raras (< 1/10.000). Dentro de cada grupo de frequências, as reações adversas são apresentadas por ordem decrescente de gravidade. **Tabela 5 Lista de reações adversas Classe de sistemas de órgãos MedDRA** Infeções e infestações **Frequência** Frequentes **Reação adversa** Conjuntivite* Herpes oral* **Classe de sistemas de órgãos MedDRA** Doenças do sangue e do sistema linfático **Frequência** Frequentes **Reação adversa** Eosinofilia **Classe de sistemas de órgãos MedDRA** Doenças do sistema imunitário **Frequência** Pouco frequentes **Reação adversa** Angioedema† **Frequência** Raros **Reação adversa** Reação anafilática, Reação da doença do soro, Reação do tipo doença do soro **Classe de sistemas de órgãos MedDRA** Afeções oculares **Frequência** Frequentes **Reação adversa** Conjuntivite alérgica* **Frequência** Pouco frequentes **Reação adversa** Queratite*¶ Blefarite*‡ Prurido ocular*‡ Olho seco*‡ **Frequência** Raros **Reação adversa** Queratite ulcerativa*¶† **Classe de sistemas de órgãos MedDRA** Afeções dos tecidos cutâneos e subcutâneos **Frequência** Pouco frequentes **Reação adversa** Erupção cutânea facial† **Classe de sistemas de órgãos MedDRA** Afeções musculosqueléticas e dos tecidos conjuntivos **Frequência** Frequentes **Reação adversa** Artralgia† **Classe de sistemas de órgãos MedDRA** Perturbações gerais e alterações no local de administração **Frequência** Frequentes **Reação adversa** Reações no local de injeção (incluindo eritema, edema, prurido, dor, inchaço e contusão) * Afeções oculares e herpes oral ocorreram predominantemente em estudos de dermatite atópica. † A frequência de prurido ocular, blefarite e olho seco era frequente e da queratite ulcerativa era pouco frequente em estudos de dermatite atópica. # Notificada pós-comercialização Dupixent 200 mg e 300 mg: Descrição de reações adversas selecionadas *Hipersensibilidade* Foram comunicados casos de reação anafilática, angioedema e de doença do soro/reações do tipo doença do soro após a administração de dupilumab (ver secção 4.4 do RCM completo). *Acontecimentos relacionados com conjuntivite e queratite* Conjuntivite e queratite ocorreram mais frequentemente em doentes com dermatite atópica que receberam dupilumab, comparado com placebo em estudos de dermatite atópica. A maioria dos doentes com conjuntivite ou queratite recuperou ou estava a recuperar durante o período de tratamento. No estudo de dermatite atópica a longo prazo OLE (AD–1225) aos três anos, as respetivas taxas de conjuntivite e queratite permaneceram semelhantes às do grupo tratado com dupilumab nos estudos de dermatite atópica controlados com placebo. Nos doentes com asma, a frequência de conjuntivite e queratite foi baixa e semelhante entre o dupilumab e o placebo. Nos doentes com CRSwNP e PN, a frequência de conjuntivite foi superior no dupilumab do que no placebo, embora menor do que a observada nos doentes com dermatite atópica. Não existiram casos de queratite notificados nos programas de desenvolvimento de CRSwNP ou PN. Entre os doentes com EoE, a frequência de conjuntivite foi baixa e semelhante entre os grupos dupilumab e placebo. Não houve casos de queratite no programa de desenvolvimento da EoE (ver secção 4.4 do RCM completo). *Eczema herpético* Foi comunicado eczema herpético em < 1% dos grupos de dupilumab e em < 1% do grupo de placebo nos estudos de monoterapia, em adultos, com dermatite atópica de 16 semanas. No estudo em adultos de dupilumab + CST de 52 semanas, foi comunicado eczema herpético em 0,2% do grupo de dupilumab + CST e em 1,9% do grupo de placebo + CST. As taxas permaneceram estáveis no estudo a longo prazo OLE (AD–1225) aos três anos. *Eosinofilia* Os doentes tratados com dupilumab tiveram um aumento médio inicial maior do que o valor basal na contagem de eosinófilos em comparação com os doentes tratados com placebo nas indicações de dermatite atópica, asma e CRSwNP. A contagem de eosinófilos diminuiu para perto dos níveis basais durante o tratamento do estudo e voltou aos valores basais durante o estudo de extensão aberto de segurança da asma (TRAVERSE). Os níveis médios de eosinófilos sanguíneos diminuíram abaixo dos níveis basais, na semana 20, e mantiveram-se, até aos 3 anos, no estudo a longo prazo OLE (AD–1225). Em comparação com o placebo, não se observou qualquer aumento na contagem média dos eosinófilos no sangue, no PN (PRIME e PRIME2). As contagens médias e medianas de eosinófilos no sangue diminuíram para perto da linha de base ou permaneceram abaixo dos níveis da linha de base na EoE (TREET Partes A e B) durante o tratamento do estudo. Foi notificado tratamento emergente para eosinofilia (≥ 5,000 células/µl) em <3% dos doentes tratados com dupilumab e < 0,5% nos doentes tratados com placebo (estudos SOLO1, SOLO2, AD–1021, DRI12544, QUEST e VOYAGE, SINUS–24 e SINUS–52, PRIME, e PRIME2, TREET Partes A e B). *Infeções* Nos estudos clínicos, em adultos, de dermatite atópica em monoterapia de 16 semanas, foram comunicadas infeções graves em 1,0% dos doentes tratados com dupilumab e em 0,5% dos doentes tratados com placebo. No estudo CHRONOS, em adultos, de dermatite atópica de 52 semanas, foram notificadas infeções graves em 0,6% dos doentes tratados com placebo e em 0,2% dos doentes tratados com dupilumab. As taxas de infeções graves permaneceram estáveis até aos 3 anos no estudo a longo prazo OLE (AD–1225). Não se observou aumento na incidência geral de infeções com dupilumab em comparação com placebo no grupo de segurança dos estudos clínicos de asma. No grupo de segurança de 24 semanas, foram notificadas infeções graves em 1,0% dos doentes tratados com dupilumab e em 1,1% dos doentes tratados com placebo. No estudo QUEST de 52 semanas, foram notificadas infeções graves em 1,3% dos doentes tratados com dupilumab e em 1,4% dos doentes tratados com placebo. Não se observou aumento na incidência geral de infeções com dupilumab em comparação com placebo no grupo de segurança dos estudos clínicos de CRSwNP. No estudo SINUS–52 de 52 semanas, foram notificadas infeções graves em 1,3% dos doentes tratados com dupilumab e em 1,3% dos doentes tratados com placebo. Não se observou qualquer aumento na incidência global de infeções com dupilumab, em comparação com o placebo, na população de segurança para ensaios clínicos de PN. Na população de segurança, foram notificadas infeções graves em 1,3% dos doentes tratados com dupilumab e 1,3% dos doentes tratados com placebo. A incidência geral de infeções foi numericamente maior com dupilumab (32,0%) em comparação com placebo (24,8%) no grupo de segurança para estudos EoE TREET (Partes A e B). No pool de segurança de 24 semanas, foram notificadas infeções graves em 0,5% dos doentes tratados com dupilumab e 0% nos doentes tratados com placebo. *Imunogenicidade* Como todas as proteínas terapêuticas, existe um potencial para imunogenicidade com dupilumab. As respostas de Anticorpos Antifármacos (AAF) não foram, de forma geral, associadas a um impacto na exposição, na segurança ou na eficácia de dupilumab. Aproximadamente 5% dos doentes com dermatite atópica, asma ou CRSwNP que receberam dupilumab 300 mg Q2W durante 52 semanas desenvolveram AAF ao dupilumab; aproximadamente 2% exibiram respostas persistentes de AAF e aproximadamente 2% apresentaram anticorpos neutralizantes. Foram observados resultados semelhantes em doentes adultos com PN que receberam dupilumab 300 mg em semanas alternadas durante 24 semanas, doentes pediátricos (6 aos 11 anos de idade) com dermatite atópica que receberam dupilumab 200 mg Q2W ou 300 mg Q4W durante 16 semanas e doentes (dos 6 aos 11 anos de idade) com asma que receberam dupilumab 100 mg Q2W ou 200 mg Q2W durante 52 semanas. Foram observadas respostas de AAF semelhantes em doentes adultos com dermatite atópica tratados com dupilumab até aos 3 anos no estudo a longo prazo OLE (AD–1225). Aproximadamente 16% dos doentes adolescentes com dermatite atópica que receberam dupilumab 300 mg ou 200 mg Q2W durante 16 semanas desenvolveram anticorpos ao dupilumab; aproximadamente 3% exibiram respostas persistentes de AAF e aproximadamente 5% apresentaram anticorpos neutralizantes. Aproximadamente 9 % dos doentes com asma que receberam dupilumab 200 mg Q2W durante 52 semanas desenvolveram anticorpos ao dupilumab; aproximadamente 4% exibiram respostas persistentes de AAF e aproximadamente 4% apresentaram anticorpos neutralizantes. Aproximadamente 1% dos doentes com EoE que receberam dupilumab 300 mg QW ou 300 mg Q2W por 24 semanas desenvolveram anticorpos para dupilumab; 0% exibiram respostas persistentes de AAF e aproximadamente 0,5% apresentaram anticorpos neutralizantes. Independentemente da idade ou população, até 4 % dos doentes nos grupos placebo foram positivos para anticorpos ao dupilumab; aproximadamente 2 % apresentaram resposta persistente de AAF e aproximadamente 1 % apresentaram anticorpos neutralizantes. Menos de 1 % dos doentes que receberam dupilumab em regime de dosagens aprovadas apresentaram respostas de AAF com titulação elevada associadas a exposição e eficácia reduzidas. Além disso, houve um doente com doença do soro e um com reação do tipo doença do soro (<0,1%) associadas a titulações elevadas de AAF (ver secção 4.4 do RCM completo). População pediátrica Dermatite atópica A segurança do dupilumab foi avaliada num estudo de 250 doentes dos 12 aos 17 anos de idade com dermatite atópica moderada a grave (AD–1526). O perfil de segurança do dupilumab nestes doentes, que foram acompanhados até a semana 16, foi semelhante ao perfil de segurança dos estudos em adultos com dermatite atópica. Asma Um total de 107 adolescentes dos 12 aos 17 anos com asma foram incluídos no estudo QUEST de 52 semanas. O perfil de segurança observado foi semelhante ao observado em adultos. Foi avaliada a segurança a longo prazo de dupilumab em 89 doentes adolescentes que foram inscritos num estudo de extensão aberto na asma moderada a grave (TRAVERSE). Neste estudo, os doentes foram acompanhados durante 96 semanas. O perfil de segurança de dupilumab no TRAVERSE foi consistente com o perfil de segurança observado nos estudos principais da asma até às 52 semanas de tratamento. Em crianças dos 6 aos 11 anos de idade com asma moderada a grave (VOYAGE), a reação adversa adicional de enterobíase foi notificada em 1,8% (5 doentes) nos grupos dupilumab e nenhuma no grupo placebo. Todos os casos de enterobíase foram ligeiros a moderados e os doentes recuperaram com tratamento anti-helmíntico sem descontinuação do tratamento com dupilumab. Em crianças dos 6 aos 11 anos de idade com asma moderada a grave, foi notificada eosinofilia (eosinófilos sanguíneos ≥3.000 células/ µl ou considerados pelo investigador como um acontecimento adverso) em 6,6% dos grupos dupilumab e 0,7% no grupo placebo. A maioria dos casos de eosinofilia foram ligeiros a moderados e não associados a sintomas clínicos. Estes casos foram transitórios, diminuíram ao longo do tempo e não levaram à descontinuação do tratamento com dupilumab. EoE Um total de 99 adolescentes entre os 12 e 17 anos com EoE foram incluídos nos estudos TREET (Partes A e B). O perfil de segurança observado foi semelhante ao observado em adultos. Segurança a longo prazo Dermatite atópica O perfil de segurança de dupilumab + TCS (CHRONOS) em doentes adultos com dermatite atópica até à semana 52 foi consistente com o perfil de segurança observado na semana 16. A segurança a longo prazo de dupilumab foi avaliada num estudo de extensão aberto em doentes dos 6 aos 17 anos de idade com dermatite atópica moderada a grave (AD-1434). O perfil de segurança de dupilumab em doentes acompanhados até à semana 52 foi semelhante ao perfil de segurança observado na semana 16 nos estudos AD–1526 e AD–1652. O perfil de segurança a longo prazo de dupilumab observado em crianças e adolescentes foi consistente com o observado em adultos com dermatite atópica. Num estudo de fase 3, multicêntrico, de extensão aberta (OLE) (AD–1225), foi avaliada a segurança a longo prazo de doses repetidas de dupilumab em 2.677 adultos com DA moderada a grave expostos a uma dose semanal de 300 mg (99,7%), incluindo 357 que completaram, pelo menos, 148 semanas do estudo. O perfil de segurança a longo prazo observado neste estudo, até aos 3 anos, foi em geral consistente com o perfil de segurança de dupilumab observado em estudos controlados. Asma O perfil de segurança do dupilumab no estudo de segurança a longo prazo de 96 semanas (TRAVERSE) foi consistente com o perfil de segurança observado nos estudos principais da asma até 52 semanas de tratamento. CRSwNP O perfil de segurança de dupilumab em adultos com CRSwNP até à semana 52 foi consistente com o perfil de segurança observado na semana 24. Notificação de suspeitas de reações adversas A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício–risco do medicamento. Pede–se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao INFARMED, I.P. Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos, Parque da Saúde de Lisboa, Av. Brasil 53, 1749–004 Lisboa, Tel: +351 21 798 73 73 Linha do Medicamento: 800222444 (gratuita) E-mail: farmacovigilancia@infarmed.pt **Data da revisão do texto:** março de 2023. Medicamento Sujeito a Receita Médica restrita. Para mais informações contactar o representante local do Titular da Autorização de Introdução no Mercado.

SANOFI – Produtos Farmacêuticos, Lda
Sede Social e Morada: Empreendimento Lagoas Park, Edifício 7 – 3º Piso 2740-244 Porto Salvo – Portugal.
Tel.: +351 213 589 400 Pessoa Colectiva nº 500 134 960. Capital Social € 26.815.015,00.

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