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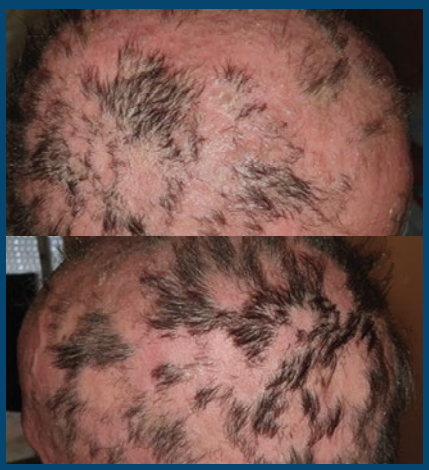

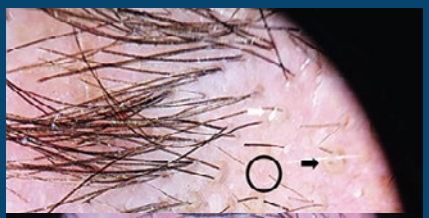

In this issue:

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PREVENÇÃO DA QUERATOSE ACTÍNICA
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AJUDA A REDUZIR VISIVELMENTE AS IMPERFEIÇÕES E MANTÉM A FUNÇÃO DA BARREIRA CUTÂNEA

3 CERAMIDAS ESSENCIAIS

NÃO COMEDOGÉNICO

HIPOALERGÉNICO, FORMULADO PARA MINIMIZAR O RISCO DE ALERGIA

SEM PERFUME

ATÉ
-21,6%
LESÕES INFLAMATÓRIAS APÓS 4 SEMANAS[1]

ATÉ
-40%
NO TAMANHO DAS LESÕES INFLAMATÓRIAS EM APENAS 3 DIAS[2]

ÁCIDO SALICÍLICO

ÁCIDO SALICÍLICO

AHAs

ARGILA HECTORITA

MVE technology — All day hydration

TECNOLOGIA MVE

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

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

LA ROCHE POSAY
LABORATOIRE DERMATOLOGIQUE

NOVO

LIPIKAR
LAIT UREA 10%

LOÇÃO HIDRATANTE DE TRIPLA AÇÃO, COM UREIA
ANTI-DESCAMAÇÃO, ANTI-RUGOSIDADE, APAZIGUANTE

[10% UREIA + MANTEIGA DE KARITÉ + HEPES + ALANTOÍNA]

INDICADO PARA **XEROSE CUTÂNEA,**
XEROSE SENIL, ICTIOSE, QUERATOSE PILAR, PSORÍASE

TEXTURA DE RÁPIDA ABSORÇÃO

EFICÁCIA COMPROVADA EM SÉNIORES, ADULTOS E CRIANÇAS

TESTADO EM PELE SENSÍVEL

XEROSE CUTÂNEA (DERMASCORE®)

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DIMINUIÇÃO SIGNIFICATIVA DA XEROSE CUTÂNEA LOGO APÓS UMA ÚNICA APLICAÇÃO

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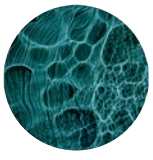
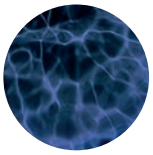


UREIA 10%
UMA MOLÉCULA ESSENCIAL PARA UMA HIDRATAÇÃO ADEQUADA E PARA PRESERVAR A INTEGRIDADE DA BARREIRA CUTÂNEA

AÇÃO HIDRATANTE
MELHORA A FUNÇÃO BARREIRA
AÇÃO QUERATOLÍTICA



HEPES
EFEITO QUERATOLÍTICO NATURAL
REFORÇA A HIDRATAÇÃO

MANTEIGA DE KARITÉ
FORTALECE A BARREIRA CUTÂNEA
NUTRE A PELE

LA ROCHE-POSAY. A EXIGÊNCIA DERMATOLÓGICA.

VICHY
LABORATOIRES

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SÉRUM B3
MANCHAS

5% NIACINAMIDA
1% ÁCIDO TRANEXÂMICO
8% COMPLEXO PEELING
[ÁCIDO GLICÓLICO + HEPES + UREIA]
VITAMINA CG

AÇÃO SINÉRGICA NAS HIPERPIGMENTAÇÕES
CLINICAMENTE COMPROVADO

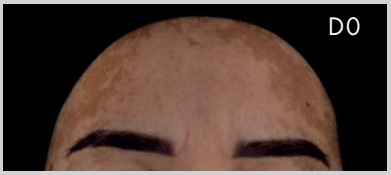
- **REDUZ AS MANCHAS ESCURAS**
- **MELHORA A TEZ DA PELE**
- **MELHORA A APARÊNCIA DA PELE**

EFICÁCIA NAS MANCHAS ESCURAS PERSISTENTES*

-38%

MASI SCORE

ANTES



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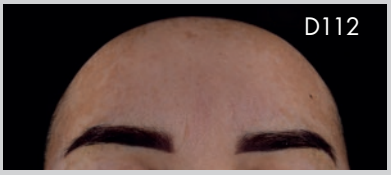

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REVIEW ARTICLE

Doxycycline prophylaxis for bacterial sexually transmitted infections: evaluating effectiveness, risks, and challenges

Profilaxia com doxiciclina para infeções sexualmente transmissíveis bacterianas: avaliando eficácia, riscos e desafios

Filipe Monteiro[1a] and João Borges-Costa[1,2,3b]*

[1]Serviço de Dermatologia, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte; [2]Clínica Universitária de Dermatologia, Faculdade de Medicina, Universidade de Lisboa; [3]Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa. Lisbon, Portugal
ORCID: [a]0009-0008-9950-1521; [b]0000-0001-8903-209X

Abstract

The increase in sexually transmitted infections (STIs) in Europe and the USA, especially among men who have sex with men (MSM) and transgender women (TW), has raised concerns and prompted the exploration of doxycycline prophylaxis as a potential intervention. Doxycycline prophylaxis can be administered either as a daily 100 mg dose (DoxyPrEP) or a single 200 mg dose post-sexual activity (DoxyPEP). Recent clinical trials, primarily focusing on higher-risk groups, have shown reductions of approximately 70% in syphilis and chlamydia infections and conflicting results regarding gonorrhea infection (up to 50%). Despite these advancements, the effectiveness of doxycycline prophylaxis among women has not been established and this strategy raises concerns about community acceptability, adverse events, safety, antimicrobial resistance, microbiome disruption, and cost-effectiveness. Ongoing clinical trials and agent-based models aim to address these uncertainties to predict the impact on a population level and on specific groups. This review aims to assess the existing data of doxycycline STI prophylaxis, identify knowledge gaps, and synthesize existing literature and guidelines about the current recommendations.

Keywords: Doxycycline. Prophylaxis. Sexually transmitted infections.

Resumo

O aumento de infecções sexualmente transmissíveis (IST) na Europa e nos EUA, especialmente entre homens que fazem sexo com homens (HSH) e mulheres transexuais (TW), levantou preocupações e levou à exploração da profilaxia com doxiciclina como uma intervenção potencial. A profilaxia com doxiciclina pode ser administrada em dose diária de 100 mg (DoxyPrEP) ou em dose única de 200 mg pós-atividade sexual (DoxyPEP). Ensaios clínicos recentes, centrados principalmente em grupos de maior risco, mostraram reduções de aproximadamente 70% nas infecções por sífilis e clamídia e resultados conflituantes em relação à infecção por gonorreia (até 50%). Apesar destes avanços, a eficácia da profilaxia com doxiciclina entre as mulheres não foi demonstrada e esta estratégia levanta preocupações sobre a aceitabilidade da comunidade, eventos adversos, segurança, resistência antimicrobiana, perturbação do microbioma e relação custo-eficácia. Os ensaios clínicos em curso e os modelos baseados em agentes visam abordar estas incertezas para prever o impacto a nível populacional e em grupos específicos. Esta revisão tem como objetivo avaliar os dados existentes sobre a profilaxia de IST com doxiciclina, identificar lacunas de conhecimento e sintetizar a literatura e as diretrizes existentes sobre as recomendações atuais.

Palavras-chave: Doxiciclina. Profilaxia. ISTs.

***Correspondence:**
Filipe Monteiro
E-mail: filipesilvamonteiro@gmail.com

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Introduction

In recent years, Europe has witnessed a concerning surge in sexually transmitted infections (STIs), reaching an alarming peak in 2019, with an increase by 9% for chlamydia, 55% for gonorrhea, and 25% for syphilis since 2015. While chlamydia remains prevalent among young women, cases have doubled among men who have sex with men (MSM). In this group, gonorrhea has been reported in 48% of the cases and syphilis in 68%, with a 44% increase of diagnoses among HIV-negative MSM individuals[1]. Moreover, a parallel pattern emerged in the USA in 2021 showing incidence increases of 4.1% in chlamydia, 4.8% in gonorrhea, and a 31.9% in syphilis[2]. The number of syphilis cases is concerning, since this infection can cause visual, auditory, or neurological complications in up to 8% of individuals[3]. Some of this increase is attributed to the reduction in condom use, as well as to the use of pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection, but is not fully explained by only these factors, raising the need to find targeted interventions to address this public health issue[4].

Prophylactic use of doxycycline is a strategy being studied to reduce the number of bacterial STIs. Doxycycline is a second-generation tetracycline with a bacteriostatic action on the ribosomal protein synthesis unit. It has a half-life of 20 h which allows a once or twice daily dosing, and presents a good safety and tolerability profile[5]. It is used for prophylaxis of other infections such as malaria[6], leptospirosis[7], or Lyme disease[8] and also used on long-term treatments for dermatological conditions such as acne[9] or rosacea[10]. In addition, it is considered the first-line treatment for chlamydia[11] and an alternative treatment for syphilis[12]. A single dose of 200 mg of doxycycline has been shown to achieve concentrations in colon and rectal tissues above the minimum inhibitory concentration (MIC) for chlamydia within 4-6 h post-dose, suggesting it may be an adequate option for prophylaxis of STIs in MSM both in the context of doxycyline pre-exposure prophylaxis (DoxyPrEP) or as doxycycline post-exposure prophylaxis (DoxyPEP)[5].

To reduce the incidence of bacterial STIs, more recent clinical trials have explored the use of doxycycline as a daily 100 mg dose (DoxyPrEP)[13] or a single 200 mg dose after condomless sex (DoxyPEP). These trials, predominantly among MSM and transgender women (TW), reported reductions of around 70% in syphilis and chlamydia infections, with varying effects on gonorrhea, ranging from approximately 50% reduction to no significant impact in some studies[14,15]. However, data regarding efficacy among women and other demographic groups have not shown benefit and remains limited[16].

There are concerns regarding STI chemoprophylaxis with doxycycline, namely, the potential development of antimicrobial resistance, adverse events, microbiome disruption and acceptance among patient and medical community. Furthermore, data on a population-level are still only obtainable from modeling studies that use multiple factors to make estimates that may differ from reality. Key questions remain about the target population, optimal dosage and formulation, efficacy across different groups, and a risk-benefit analysis[17]. Several studies and guidelines are in development, with a concerted effort to introduce this strategy to reduce the incidence of STIs, and the Centers for Disease Control and Prevention (CDC) solicited public input in October 2023 for the recently developed guidelines on doxycycline prophylaxis for bacterial STIs[18].

This review article aims to assess the knowledge on doxycycline STI prophylaxis, identify knowledge gaps, the existing literature, and current recommendations.

Published data on efficacy

Prophylactic use of doxycycline for STIs has shown efficacy in four open-label trials, specifically among MSM and TW (Table 1). This effectiveness extends to individuals with or without HIV infection, engaging in condomless sex, and having had a history of at least one STI in the past year.

Studies using a single 200 mg dose of doxycycline within 24-72 h after condomless sex have shown a reduction in chlamydia and syphilis infections by approximately 50-70% and the potential to reduce gonorrhea infections by around 40-50% in certain settings[13-15]. The pilot study conducted by Bolan et al. in 2015 showed a significant success in reducing bacterial STIs among MSM living with HIV and with a history of syphilis recurrence. Participants were divided into two groups: one receiving a daily 100 mg dose of doxycycline, while the other engaged in contingency management, with monetary incentives for STI-free behavior. Despite the small sample (n = 30), the DoxyPrEP group exhibited an impressive 73% reduction in bacterial STIs over the 48-week follow-up period[13].

Following this study, trials involving MSM and TW were conducted to evaluate the effectiveness of 200 mg doxycycline (DoxyPEP) as a post-exposure treatment to reduce bacterial STIs. These trials

Table 1. Clinical trials on doxycycline prophylaxis for bacterial STIs

Study	Design	Participants	Interventions	Primary endpoint	Follow-up
Bolan et al.[13] (2015)	Open-label RCT	30 HIV+ MSM who had syphilis ≥ 2 times since HIV diagnosis	Daily 100 mg doxycycline (n = 15) vs. contingency management (n = 15)	Contraction of syphilis, gonorrhea or chlamydia	48 weeks
ANRS IPERGAY[14] (2018)	Open-label RCT	232 MSM or TW on HIV PrEP and condomless sex with men	200 mg doxycycline once within 72 h after condomless sex (n = 116) vs. no doxycycline prophylaxis (n = 116)	Occurrence of a first STI during 10-month follow-up	Median time 8.7 months
DUHDS trial[20] (2021)	Open-label RCT	52 MSM on HIV PrEP with prior diagnosis of syphilis	Immediate (n = 26) vs. deferred (n = 26) daily doxycycline 100 mg	STI diagnosis	48 weeks
DoxyPEP[15] (2023)	Open-label RCT	501 MSM or TW on HIV PrEP or HIV+ who had bacterial STI last year	200 mg doxycycline once within 72 h after condomless sex (n = 339) vs. standard care (n = 162)	Incidence of STIs per follow-up quarter	Median time 270 days
DOXYVAC[21] (2023)	Open-label RCT	502 MSM on HIV PrEP who had bacterial STI last year	200 mg doxycycline once within 72 h after condomless sex (n = 332) vs. no doxycycline prophylaxis (n = 170) and 4CMenB vaccine vs. no vaccine (1:1)	Incidence of first episode of a STI	Median time 9 months
dPEP-KE[16] (2023)	Open-label RCT	449 women on HIV PrEP	200 mg doxycycline once within 72 h after condomless sex (n = 224) vs. standard care (n = 225)	Incidence of chlamydia, syphilis or gonorrhea	12 months

Study	Findings	Limitations
Bolan[13] (2015)	At week 48, diagnosis of any studied bacterial STI had an OR = 0.27 (95% CI: 0.09-0.83; p = 0.02) for the doxycycline group.	Open-label study Short follow-up Small sample
ANRS IPERGAY[14] (2018)	DoxyPEP vs. no-DoxyPEP: Time to first STI had HR = 0.53 (95% CI: 0.33-0.85; p = 0.008); Time to first chlamydia episode had HR = 0.30 (95% CI: 0.13-0.70; p = 0.006); Time to first syphilis episode had HR = 0.27 (95% CI: 0.07-0.98; p = 0.047); No significant differences were observed for gonorrhea (HR = 0.83; 0.47-1.47; p = 0.52).	Open-label study Short follow-up
DUHDS TRIAL[20] (2021)	Immediate vs. deferred arm at 24 weeks: Chlamydia infection (rate 0 vs. 81.63/100 PY, p = 0.001); Syphilis infection (rate 0 vs. 8.16/100 PY, p = 0.98); Gonorrhea infection (rate 31.37 vs. 57.14/100 PY, p = 0.505); Only 1 gonorrhea infection after 24 weeks in each arm.	Open-label study Short follow-up Small sample
DOXYPEP[15] (2023)	In the HIV PrEP cohort, 10.7% Doxy-PEP vs. 31.9% no-DoxyPEP had a STI (RR = 0.34; 95% CI: 0.24-0.46; p < 0.001). In the HIV+ cohort, 11.8% Doxy-PEP vs. 30.5% no-DoxyPEP had a STI (RR = 0.38 95% CI: 0.24-0.60; p < 0.001).	Open-label study Short follow-up
DOXYVAC[21] (2023)	Lower incidence for all studied bacterial STIs on DoxyPEP group: Chlamydia (HR = 0.11; 95% CI: 0.04-0.30, p < 0.0001), incidence of 2.1/100 PY vs. 19.3/100 PY; Syphilis (HR = 0.21; 95% CI: 0.09-0.47, p < 0.001), incidence of 3.4/100 PY vs. 16.3/100 PY; Gonorrhea (HR = 0.49; 95% CI: 0.32-0.76, p = 0.001), incidence of 20.5/100 PY vs. 41.3/100 PY; *Mycoplasma genitalium* (HR = 0.55; 95% CI: 0.34-0.89, p = 0.015), incidence of 16.8/100 PY vs. 29.4/100 PY.	Open-label study Short follow-up
dPEP-KE[16] (2023)	DoxyPEP group vs. standard of care in STI incidence with no significant differences (RR = 0.88; 95% CI: 0.60-1.29; p = 0.51) with 25.1 vs. 29.0/100 PY. Chlamydia accounted for 78.0% of STIs; no difference between groups (RR = 0.73; 95% CI: 0.47-1.13).	Open-label study Short follow-up

CI: confidence interval; DoxyPEP: Doxycycline Post-exposure Prophylaxis; HIV: human immunodeficiency virus; HR: hazard ratio; MSM: men who have sex with men; OR: odds ratio; PrEP: pre-exposure prophylaxis; PY: person-year; RCT: randomized controlled trial; RR: relative risk; STI: sexually transmitted infection; TW: transgender women.

recruited participants with a history of STIs in the previous year, including individuals living with HIV or utilizing HIV PrEP. Notably, one study published in 2018 – the ANRS IPERGAY – enlisted 232 participants for an open-label randomized controlled trial to compare DoxyPEP to standard-care for bacterial STI treatment. The DoxyPEP group exhibited a 47% relative reduction in the incidence of new STIs. Furthermore, in the intention-to-treat analysis, there was a substantial 70% relative reduction in the risk of chlamydia infection and a 73% relative reduction in the risk of syphilis, with no notable differences observed for gonorrhea infection. In this study, the lack of effectiveness against this infection was linked to local resistance of *Neisseria gonorrhoeae* to tetracyclines[14]. Of note there is a substudy of this population where the authors confirmed that the prevalence of *Mycoplasma genitalium* infection remained stable at the 6-month follow-up, with no significant differences observed between the DoxyPEP arm and the no-DoxyPEP arm, indicating that prophylaxis also had no discernible impact on the incidence of this STI[19].

The DUHDS trial findings on MSM receiving daily 100 mg doxycycline were presented at the 2021 Conference on Retroviruses and Opportunistic Infections and recruited 52 participants who were randomly assigned to immediate or deferred doxycycline prophylaxis after 24 weeks. Doxycycline chemoprophylaxis on both groups reduced the probability of acquiring any STI with an odds ratio (OR) of 0.18 (95% confidence interval [CI]: 0.05-0.68) and also lowered the rate of chlamydia infection, but its impact on syphilis could not be determined, probably due to the limited sample size and short follow-up[20].

In the DoxyPEP trial (2023), 501 participants were randomly assigned in a 2:1 ratio to either take 200 mg of doxycycline within 72 h after condomless sex or to receive standard care without doxycycline. The included participants were MSM or TW on HIV pre-exposure prophylaxis (PrEP) or HIV positive (HIV+) individuals who had experienced a bacterial STI in the previous year. On those on HIV PrEP, the relative risks (RR) were 0.45 (95% CI, 0.32-0.65) for gonorrhea, 0.12 (95% CI, 0.05-0.25) for chlamydia, and 0.13 (95% CI, 0.03-0.59) for syphilis. In the HIV+ cohort, the relative risks were 0.43 (95% CI, 0.26-0.71), 0.26 (95% CI, 0.12-0.57), and 0.23 (95% CI, 0.04-1.29), respectively. Compared to the previous studies, prophylaxis demonstrated some efficacy against gonorrhea incidence (around 50%) with an overall reduction of approximately two-thirds in bacterial STI incidence[15].

In the DOXYVAC trial (2023), efficacy in reducing bacterial STIs among high-risk MSM on HIV PrEP was also evident. This study randomized participants into DoxyPEP or standard-care in a 2:1 ratio. On an unblinded early interim analysis a notable 65% reduction in STI incidence was observed and all participants were offered DoxyPEP, with the initial 9-month follow-up period showing significant reductions in chlamydia by 89%, syphilis by 79%, gonorrhea by 51%, and *M. genitalium* by 45%[21].

When considering other populations, only one trial has provided data, indicating a lack of efficacy in women. The dPEP-KE (2023) involved 449 women in Kenya who were on HIV PrEP, and randomly assigned them to receive a single 200 mg dose of doxycycline within 72 h after engaging in condomless sex or the standard care. After a year of follow-up, no significant differences were observed in STI incidence between the groups. While participant-reported adherence was moderately high, the results of doxycycline testing in hair indicated that 44% of those assigned to receive DoxyPEP may not have taken any doxycycline[16]. Doxycycline in vaginal secretions peaks around 8 h after a 200 mg dose and remains at inhibitory levels against syphilis and chlamydia for 3-4 days post-dosing, and around 2 days for gonorrhea[22]. This suggests that doxycycline should be effective also for women but adherence may have been a significant problem. In addition, this trial found that all *N. gonorrhea* isolates were resistant to tetracyclines, potentially contributing to the lack of efficacy of the intervention[16].

Ongoing clinical trials are actively trying to determine the concentration levels achieved in body fluids and compare different outcomes of interventions with DoxyPEP and DoxyPrEP, as summarized in table 2[23-28].

Several additional studies have been using mathematical models of transmission to assess potential efficacy[29-31]. One study used a model to assess the impact of syphilis within an MSM population using doxycycline 100 mg daily, assuming an use effectiveness of 70% on 50% of MSM. It projected a reduction on incidence of syphilis cases by 49% within a 12-month period and by 85% over a span of 10 years. In addition, it suggested that the greatest preventive impact would be by targeting subpopulations of men with higher sexual activity[29]. Another study using electronic health records of 10,546 MSM and TW with a history of ≥ 2 STI tests determined that if DoxyPEP were prescribed to all individuals, it would prevent 71% of STI diagnoses, with a number needed-to-treat (NNT) of 3.9 to avert one STI diagnosis/year. However, targeting specific subgroups,

Table 2. Ongoing clinical trials

Study ID	Design	Participants	Interventions	Primary endpoints	Estimated follow-up
DOXY-PK[23] NCT06007534 2023	Open-label	MSM on HIV PrEP taking doxycycline for STI prevention (n = 25)	Blood and urine samples, oropharyngeal swabs and hair samples before and after taking 200 mg of doxycycline	Concentration of doxycycline in collected samples	6 months
Project PEACH[24] NCT05072093 2021	Open-label	MSM followed at PRISM Health Research Clinic (n = 200)	DoxyPEP after condomless sex in a single 200 mg dose within 72 h	Change in STI diagnoses from baseline at 12 and 24 months	2 years
Combo-PEP[25] NCT04860505 2021	Open-label	HIV negative person reporting sex with another man in the last year (n = 20)	Doxycycline and bictegravir, emtricitabine and tenofovir alafenamide simultaneous intake 1 h before specimen collection	Plasma, rectal and vaginal doxycycline concentration	12 months
Syphilaxis[26] NCT03709459 2019	Observational	MSM who have had ≥ 2 screenings for syphilis, chlamydia and gonorrhea in the past 12 months, and at least one episode of syphilis in the past 2 years (n = 100)	Doxycycline 100 mg/day for 12 months duration	Incidence of STI per 100 PY. Patterns of use and adherence	12 months
DOXY-PEP (Atlanta)[27] NCT05853120 2023	Open-label RCT	Healthy male or female people (n = 40)	Doxycycline 100 mg or 200 mg taken on days 0, 3, 7 and 10	Doxycycline concentration in vaginal and rectal tissues	8 weeks
DISCO[28] NCT04762134 2023	Open-label RCT	MSM with > 1 male partner and previous diagnosis of STI in the past 12 months (n = 560)	Doxycycline 100 mg orally daily for 12 months vs. doxycycline 200 mg orally once within 72 h following condomless sex	Plasma doxycycline levels. Frequency of STIs over time	60 weeks

HIV: human immunodeficiency virus; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; PY: person-year; RCT: randomized controlled trial; STI: sexually transmitted infection.

there would be a lower NNT for HIV PrEP users or HIV+ people (NNT = 2.9), averting 60% of STI diagnoses, and for individuals with a history of STI within the previous year (NNT = 2.4), averting 39% of STI diagnoses. DoxyPEP on those with repeated or recent STIs improved efficiency (lower NNTs) but prevented fewer STIs due to lower population coverage, concluding that strategies based on STI history rather than HIV status or PrEP use were more efficient. While promoting DoxyPEP to a wider population would prevent more STI diagnoses, limiting it to high-risk groups would minimize DoxyPEP usage while maximizing its benefit[30]. An additional study using an agent-based model on a population of 10,230 MSM determined that if a 20% uptake and 80% adherence level of DoxyPEP were achieved, a 10% reduction in syphilis infections would occur over a decade, amounting to 57 fewer cases/1000 individuals, and a 22% reduction of infections in situations where condoms were not used or had failed. This model suggests a moderate impact on syphilis incidence and considered DoxyPEP as a secondary prevention measure alongside condoms and improved syphilis screening[31].

In terms of the impact on antibiotic usage, a study projected an increase of approximately 2.52 million monthly doses, underscoring that while doxycycline prophylaxis may lead to a reduction in STIs, it is anticipated to elevate overall doxycycline consumption, despite the concurrent decrease in antibiotics used for treating these infections[32].

While doxycycline prophylaxis shows effectiveness in reducing bacterial STIs, especially in high-risk groups, there is a potential for it to contribute to a rise in overall antibiotic usage, and model-based studies are yet to definitively determine its impact on a population level.

Community acceptability

The effectiveness of public health strategies among MSM, such as bacterial STI prevention using doxycycline prophylaxis, depends on community and healthcare provider acceptance for success. Several studies, primarily based on surveys or interviews, indicate that the use of doxycycline for preventing bacterial STIs is generally accepted among MSM[33-36].

Before the awareness of recent trials regarding DoxyPEP efficacy, an online survey targeting MSM in Australia studied the potential acceptability of syphilis chemoprophylaxis. Among the 2095 participants surveyed, 52.7% (95% CI: 50.6-54.8%) expressed likelihood to use chemoprophylaxis to the lower their risk of acquiring syphilis. This percentage notably increased to 75.8% (95% CI: 74.0-77.6%) if chemoprophylaxis was shown to help reduce infections within this community[29]. Also in Australia, another online survey on 1347 MSM identified 54.3% willing to use DoxyPrep and linked willingness to participants with high number of sexual partners (> 10), recent methamphetamine use, being conscious about avoiding STIs, having a history of more STIs since starting HIV PrEP, and using condoms only on a partner's request[33]. In China, an online survey on 725 participants verified that willingness to use syphilis chemoprophylaxis was greater among those without a history of prior doxycycline use ($p = 0.009$). Among respondents, 67.8% preferred a post-exposure strategy, while 60.0% expressed concerns about potential side effects as their primary worry[34]. In Canada, 424 MSM completed a questionnaire during routine STI clinic visits and results showed that 60.1% and 44.1% were likely to use DoxyPEP or DoxyPrEP, respectively. The study identified several factors associated with this compliance. For DoxyPrEP, factors included a belief of being at risk for syphilis (OR = 1.6; 95% CI: 1.0-2.5), previous or current HIV PrEP use (OR = 2.2; 95% CI: 1.1-4.3), and a high level of concern about STI acquisition (OR = 1.9; 95% CI: 1.0-3.4). Regarding DoxyPEP, willingness was associated with a higher number of diagnosed STIs (OR = 1.4; 95% CI: 1.2-1.7). Participants' subjective assessments of STI risk had more impact on considering doxycycline prophylaxis rather than traditional epidemiological risk factors, such as the total number of sex partners or a prior history of syphilis. Notably, 89% of participants were aware of antimicrobial resistance, but this did not influence the acceptability of doxycycline prophylaxis[35]. In the US, a similar willingness trend was observed on 212 MSM that answered an online survey with 67.5% indicating they would consider taking doxycycline prophylaxis if recommended by their provider, especially those with recent diagnosis of bacterial STI (OR = 2.8, 95% CI: 1.22-6.45, $p = 0.02$) or using HIV PrEP (OR = 3.7, 95% CI: 1.64-8.24, $p \leq 0.01$)[36]. This survey also included health-care providers, with 89.5% expressing readiness to prescribe doxycycline PrEP/PEP if recommended by the CDC, but only 43.4% willing to do so without this guidance. Both community and healthcare participants exhibited concern regarding potential drug resistance[36].

Until recently, despite lacking formal guidelines, prophylaxis for bacterial STIs was already being employed as an off-label strategy in some instances. An online survey involving 96 MSM in Germany revealed that 23% reported prior use of doxycycline as DoxyPEP and 6% as DoxyPrEP, most individuals having obtained the pills from leftover supplies of previous doxycycline treatments[37]. In Melbourne, Australia, 9.9% of 1065 MSM participating in a survey also admitted using doxycycline prophylaxis within the previous month[38]. In London, UK, a similar tendency was observed in 8% of 106 participants from a survey conducted in a sexual health clinic, admitting using antibiotics as a preventive measure against STIs and 75% of those specifically utilizing doxycycline, with half of them using antibiotics on a daily basis[39].

These studies have indicated that the general public is inclined to view doxycycline prophylaxis as a safe and acceptable intervention. Following a trajectory similar to HIV PrEP, the utilization of antibiotics for preventing bacterial STIs may have a rise in adoption among MSM and other populations and already shows signs of off-label usage by some whether prescribed or not. If challenges such as antimicrobial resistance or other issues arise, reversing this trend could prove to be difficult. Given its confirmed efficacy, ensuring the supervised use of doxycycline may be preferable to guarantee optimal effectiveness and safety.

Adverse events and safety profile

Doxycycline is generally considered safe and well-tolerated, yet adverse effects have been identified in clinical trials using this drug. Commonly reported side effects include the gastrointestinal tract and skin. Caution is advised, particularly avoiding its use during pregnancy and breastfeeding due to teratogenic risks[5].

Regarding clinical trials using doxycycline prophylaxis for bacterial STIs, adverse events were mostly mild and discontinuation due to these was relatively

low. In the trial conducted by Bolan et al., only one patient needed to discontinue the 100 mg daily doxycycline treatment by week 29 due to gastroesophageal reflux, with no serious adverse events reported[13]. In the ANRS IPERGAY study, serious adverse events occurred at similar rates between the studied groups, with no reported deaths among participants. Those on DoxyPEP had a median doxycycline usage of 680 mg/month, displaying a favorable safety profile overall, but there was an elevated occurrence of gastrointestinal adverse events compared to the HIV PrEP-only group (25% vs. 14%; p = 0.03). In particular, eight individuals (7%) in the DoxyPEP group discontinued doxycycline due to drug-related adverse events[14]. During the relatively short observation period of the DoxyPEP trial, no significant changes in weight were observed under doxycycline intake when compared to the control group and no serious adverse events were reported. A mere 2% of participants opted to discontinue doxycycline due to its adverse effects[15]. In the dPEP-KE study, participants experienced no serious adverse events attributable to doxycycline use. The most prevalent adverse effect was nausea, reported in 7.2% of follow-up visits in the DoxyPEP group and 4.6% in the standard-care group, with only 2.7% of participants discontinued the study due to adverse effects associated with the drug[16].

Adverse events due to prolonged doxycycline use are frequently reported, but severe side effects leading to discontinuation are rare. Overall, long-term use is deemed safe[40]. The majority of studies are focused on daily doxycycline use, but most bacterial STI chemoprophylaxis research explores mainly the use of doxycycline in the form of DoxyPEP, representing intermittent rather than daily administration. One hypothesis that may underlie this approach is that intermittent doxycycline use might potentially result in fewer side effects and reduced risk of antimicrobial resistance when compared to DoxyPrEP[40].

Antimicrobial resistance and microbiome disruption

Due to the rapid development of resistances by *N. gonorrhoeae*, antimicrobial resistance is one of the main concerns regarding the use of doxycycline for prophylaxis of bacterial STIs[17], and several genes related to tetracycline resistance have already been identified, like the plasmid-encoded tetM gene and the mutations in chromosomal genes such as rpsJ, porB, and the mtr operon[41]. A study using whole genome sequencing data and MICs from a pool of 5644 *N. gonorrhoeae* isolates found that the selection for plasmid-encoded and chromosomally encoded tetracycline resistance was influenced by the antimicrobial resistance profiles. In isolates with plasmid-encoded resistance to tetracyclines, MICs to other antimicrobials were lower when compared to isolates with low-level tetracycline resistance. It was observed as well that isolates with tetracycline MICs ranging from 2 to 8 μg/ml also had higher MICs for ceftriaxone, azithromycin, and ciprofloxacin when comparing to non-tetracycline-resistant isolates ($p < 0.0001$). Co-resistance to tetracycline and azithromycin was associated with chromosomally encoded mutations and in 12.9% of plasmid-encoded tetM isolates there was a co-resistance of tetracycline and ciprofloxacin. Although tetracycline and ceftriaxone resistance is uncommon, it is most likely due to strains with chromosomally mediated tetracycline resistance, like those with the *penA* 60 allele. This data indicate that the population of *N. gonorrhoeae* exhibiting intermediate MICs could serve as a reservoir for rapid resistance evolution and DoxyPEP may select tetracycline-resistant lineages that also resist to other antimicrobials. However, if DoxyPEP primarily favors lineages with tetM-mediated resistance, it may decrease *N. gonorrhoeae* resistance to other antimicrobials because of the lower co-resistance in these lineages[41]. The prevalence of the tetM gene in certain populations is significant, as observed by a study involving 50 endocervical swab specimen's positive for *N. gonorrhoeae* from women in Kenya. In this study, the American-type plasmid-mediated tetM gene was identified in 96% of the samples, suggesting that DoxyPEP for STI prevention might have limited efficacy against gonorrhea in sub-Saharan Africa[42].

Tetracycline resistance on gonorrhea or *M. genitalium* has also been observed on efficacy clinical trials. In the ANRS IPERGAY trial, among positive gonorrhea isolates, 7 out of 9 exhibited resistance or intermediate resistance to tetracyclines with molecular testing identifying the tetM gene in one of the resistant isolates, as well as the Val57Met mutation in the rpsJ gene and mutations associated with the overexpression of the antibiotic efflux pump MtrCDE on all resistant isolates[14]. In a sub-study of this population, 210 participants underwent testing for *M. genitalium*, and their isolates were examined for antimicrobial resistance patterns. The infection's prevalence was found to be 10.5%, with isolates exhibiting resistance to azithromycin in 66.7%, fluoroquinolones in 9.1%, and tetracyclines in 12.5% (linked to an *in vivo* mutation of 16S rRNA). Importantly, no significant differences were observed between the

DoxyPEP and no-DoxyPEP arms[19]. In terms of tetracycline resistance among *N. gonorrhoeae* isolates from the DoxyPEP trial, participants baseline resistance stood at approximately 27% changing later to 38% in the doxycycline group and 12% in the standard-care group. This study, however, did not investigated whether resistant isolates became more prevalent due to doxycycline[15]. Finally, as expected for the sub-Saharan Africa, in the dPEP-KE study, the prevalence of the tetM gene in *N. gonorrhea* was 100% both at baseline and during follow-up visits in both the doxycycline-PEP group and the standard-care group. In this population, none of the 76 tested *C. trachomatis* samples exhibited the tet(C) gene cassette, also correlated to tetracycline resistance[16].

To explore the impact of DoxyPEP on gonorrhea transmission among MSM populations a study used a deterministic compartmental model with various uptake levels (10-75%) and a 20-year prevalence and resistance dynamics against a baseline scenario without DoxyPEP. Results indicated that DoxyPEP initially reduced gonorrhea prevalence and incidence, but accelerated the spread of doxycycline resistance, leading to the loss of clinical efficacy within 20 years. This initial reduction in infection prevalence was constrained by existing doxycycline-resistant strains in the population and doxycycline promoted the spread of resistant strains already present, rather than causing de novo resistance emergence. Moreover, while high DoxyPEP use (50-75%) initially reduced ceftriaxone treatments by over 50% in the first 5 years compared to the baseline, this reduction narrowed to 17.6% after 20 years. Increasing DoxyPEP uptake and higher initial doxycycline resistance prevalence accelerated the loss of efficacy and had minimal impact on extending the clinical lifespan of ceftriaxone for *N. gonorrhoeae* treatment. The model suggested that while DoxyPEP is effective in the short-term its reduction in cumulative infections was only around 13.5-14.6% at 20 years, and it hastens doxycycline resistance to 87% within 1.8-14.1 years, depending on uptake (10-75%)[43].

Regarding the impact on microbiome disruption, one systematic review studied the impact of oral tetracycline-class antibiotics on normal bacterial flora. The analysis included seven randomized controlled trials among adults, comparing daily oral tetracycline-class antibiotics versus non-tetracycline treatments. Most studies used doxycycline at 100-200 mg/day over 2-18 weeks, as well as other antibiotics of the same class. The outcomes revealed that oral tetracycline usage generally increased tetracycline-resistant strains in the body's normal flora. Subgingival flora exhibited a slight rise in tetracycline resistance during short-term therapy (2 weeks).

Gastrointestinal studies on stool cultures initially showed increased resistance in commensal *Escherichia coli*, but resistance levels returned to baseline 2 weeks after a 3-week course of 100 mg/day of doxycycline. Extended doxycycline use for 13 weeks heightened resistance in the upper respiratory flora, increasing the MIC by 3.74, and individuals were also 5.77 times more likely to harbor doxycycline-resistant isolates (95% CI: 1.40-23.74, p = 0.02). Conversely, the included studies showed skin flora did not display changes in *Cutibacterium acnes* tetracycline resistance after 18 weeks of oxytetracycline/minocycline treatment. While these antibiotics slightly increased resistance in specific floras, they had minimal impact on resistance to non-tetracycline antibiotics.

Overall, although these effects were modest and short-lived, limited data from small-scale studies suggest that oral tetracyclines used for 2-18 weeks may elevate resistance in some specific floras but do not seem to have significant impact on resistance to other non-tetracycline class antibiotics in commensal bacteria[44].

The DoxyPEP trial also investigated microbiome impact by studying *Staphylococcus aureus* carriage in participants. An initial positivity of 45%, with 12% of strains resistant to doxycycline was compared after 12 months of follow-up. Carriage of *S. aureus* was prevalent on 28% of the doxycycline user group, in comparison to 47% of the control group (p = 0.03), including 16% vs. 8% isolates resistant to doxycycline. However, the proportion of participants positive for carriage of doxycycline-resistant *S. aureus* remained similar between groups (5% in the DoxyPEP group vs. 4% in the control group)[15].

Collectively, studies suggest that antimicrobial resistance poses a substantial challenge for *N. gonorrhoeae*, raising concerns about a potential failure of DoxyPEP in addressing this infection and an increased risk of antimicrobial resistances development. Studies also highlight alterations in the microbiome's antimicrobial resistance patterns due to prophylactic use of doxycycline. However, the actual impact on health outcomes at a population level remains unclear.

Conclusion

DoxyPEP is acknowledged by current guidelines as a strategy for reducing the burden of bacterial STIs among at-risk populations. The European AIDS Clinical

Society, in its 2023 guidelines update, has introduced new recommendations indicating that the consideration of DoxyPEP can be proposed to individuals with recurrent STIs who are living with HIV or are on HIV PrEP on a case-by-case basis[45]. On 2023, the Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine (ASHM) released a consensus statement regarding the use of DoxyPEP in Australia. Within the Australian context, it highlighted that among bacterial STIs, syphilis stands as the primary cause of morbidity among MSM, while chlamydia and gonorrhea seldom lead to complications in this population, recommending DoxyPEP primarily for preventing syphilis in at-risk MSM. The ASHM also acknowledges a potential indirect benefit for the broader community, particularly for women who also engage in sexual activities with MSM, as this demographic faces a higher risk of complications. However, there is no evidence supporting this conclusion[46]. Recently, the CDC published guidelines regarding the use of doxycycline prophylaxis for bacterial STIs and requested a public input to address any concerns related to these. The draft version recommends the use of DoxyPEP as a single 200 mg oral dose of doxycycline within 72 h of oral, vaginal, or anal sex for MSM or TW with a history of at least one bacterial STI in the past 12 months and who continue to be at risk for bacterial STI acquisition or for those engaging in sexual activities known to increase the likelihood of STI exposure. The guidelines emphasized a maximum daily dose of 200 mg, and screening for bacterial STIs and HIV to be conducted every 3-6 months following the initial use of DoxyPEP[47].

DoxyPEP presents a targeted and tailored approach to preventing bacterial STIs, focusing on individuals at high risk, such as MSM living with HIV, those on HIV PrEP, or those with multiple risk factors. The potential expansion of its role to include women demands careful study to address concerns of equity, especially given the significant impact of these diseases on women's reproductive health. While DoxyPEP likely reduces the incidence of syphilis and chlamydia, implementing it requires an investigation of the potential adverse effects, alterations to the microbiome, and antimicrobial resistances. As the global incidence of bacterial STIs continues to rise, the introduction of doxycycline prophylaxis may have a role on reverting this trend.

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Conflicts of interest

None.

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

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

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REVIEW ARTICLE

Omalizumab and new therapeutic targets in chronic spontaneous urticaria

Omalizumab e novos alvos terapêuticos na urticária espontânea crónica

Ana S. Pereira[1a], Joana Xará[1b], Duarte Flor[1c], and Margarida Gonçalo[2d]*

[1]Department of Dermatology, Coimbra University Hospital; [2]Faculty of Medicine, University of Coimbra. Coimbra, Portugal
ORCID: [a]0000-0003-4930-4614; [b]0000-0002-7041-292X; [c]0000-0003-4785-0478; [d]0000-0001-6842-1360

Abstract

Chronic spontaneous urticaria (CSU) is a common and distressing skin disease characterized by itchy wheals, angioedema, or both. There is currently no cure for CSU and symptomatic treatment is often insufficient. Omalizumab, a humanized anti-immunoglobulin (Ig) E monoclonal antibody, remains the only biological drug licensed for CSU, almost a decade after its approval. However, growing knowledge of the pathophysiological mechanisms of this disease has led to recent advances in its treatment, with several drugs in investigation both in pre-clinical and clinical settings. These include biologicals, such as dupilumab (anti-IL-4Rα), secukinumab (anti-IL-17), tezepelumab (anti-TSLP), ligelizumab (anti-IgE), lirentelumab (anti-Siglet 8), and barzovolimab (anti-cKIT), as well as "small molecules," such as Bruton tyrosine kinase (BTK) inhibitors (remibrutinib) and a Mas-related G protein-coupled receptor X2 (MRGPRX2) antagonist. Here, we review the current and future therapeutic options for CSU, based on what is known about the pathogenesis of the disease.

Keywords: Chronic spontaneous urticarial. Mast cells. Omalizumab. Novel biologics. Small molecules.

Resumo

A urticária crónica espontânea (UCE) é uma dermatose comum e angustiante caracterizada por pápulas pruriginosas, angioedema ou ambos. Atualmente, não existe cura para a UCE e o seu tratamento sintomático é frequentemente insuficiente. O Omalizumab, um anticorpo monoclonal humanizado anti-IgE, continua a ser o único fármaco biológico licenciado para a UCE, quase uma década após a sua aprovação. No entanto, o conhecimento crescente dos mecanismos fisiopatológicos desta doença conduziu a recentes avanços no seu tratamento, com vários fármacos em investigação, tanto em contexto pré-clínico como clínico. Estes incluem medicamentos biológicos, como o dupilumab (anti-IL-4Rα), o secukinumab (anti-IL-17), o tezepelumab (anti-thymic stromal lymphopoietin [TSLP]), o ligelizumab (anti-IgE), o lirentelumab (anti-Siglet 8) e o barzovolimab (anti-cKIT), bem como "pequenas moléculas," como os inibidores da tirosina quinase de Bruton (BTK) (Remibrutinib) e um antagonista do recetor X2 acoplado à proteína G relacionado com Mas (MRGPRX2). Neste trabalho, revemos as opções terapêuticas atuais e futuras para a UCE, com base no conhecimento atual sobre a patogénese da doença.

Palavras-chave: Urticária crónica espontânea. Mastócitos. Omalizumab. Biológicos. Pequenas moléculas.

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

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Introduction

Chronic spontaneous urticaria (CSU) is a common skin condition characterized by the development of itchy hives, angioedema, or both, with no recognizable triggers, lasting for a minimum of 6 weeks. It affects approximately 1% of the population worldwide[1,2] with women being affected almost twice as frequently as males and a peak age at first symptoms between 20 and 40 years old[3].

Although spontaneous remission is expected after an average period of 2-5 years[4], extended periods of up to 10 years have been reported[5]. Moreover, CSU has a marked negative burden both on the patient and society due to the unpredictability of attacks, sleep deprivation, reduced performance at work or school, and limitation of social life and sexual dysfunction[1]. Thus, early, effective, and safe treatment is essential for this disease.

There are no curative treatments for CSU and current therapies aimed at symptomatic control are insufficient for many patients[3]. The first-line standard-dose or up-dosed 2nd-generation H1-antihistamine (H1-AH) is effective in less than half of CSU patients[6], whereas the only other approved drug for CSU – the anti-immunoglobulin (Ig) E monoclonal antibody (mAb) omalizumab (OMA) – has a complete response rate under 70% according to real-world data[7]. Other medications such as cyclosporine, hydroxychloroquine, dapsone, and methotrexate are used off-label with variable efficacy[8]. In this context, the development of novel therapeutic options for CSU with increased efficacy is highly needed.

Encouraged by our growing understanding of the pathophysiology of CSU, several new treatment options are currently being studied in pre-clinical and clinical settings. These comprise biologicals, such as dupilumab (anti-IL-4Rα), secukinumab (anti-IL-17), tezepelumab (anti-TSLP), ligelizumab (anti-IgE), lirentelumab (anti-Siglet 8), and barzovolimab (anti-cKIT), and other drugs classified as "small molecules" in which Bruton tyrosine kinase (BTK) inhibitors (such as remibrutinib) and a Mas-related G protein-coupled receptor X2 (MRGPRX2) antagonist are included.

The aim of this work is to review the current and future therapeutic options for CSU that is targeting recognized pathophysiological mechanisms of the disease.

Basic pathogenesis of CSU

Urticaria occurs due to the activation and degranulation of mast cells and basophils, with consequent release of histamine, proteases, cytokines, platelet-activating factor (PAF), and other arachidonic acid metabolites (prostaglandin D2, leukotrienes C4, D4, and E4)[3,9]. These substances promote vasodilatation and increased capillary permeability, responsible for the hives and angioedema, as well as sensory nerve stimulation, which contributes to swelling, redness, and pruritus[3].

Regarding CSU, autoimmunity and/or autoallergy are the main pathophysiological mechanisms involved in mast cell degranulation, but direct activation of mast-cell receptors as well as other inflammatory pathways together with the activation of the coagulation and complement cascades may also be involved in the development of lesions and symptoms of urticaria.

Autoimmunity and/or autoallergy

Two different subtypes of CSU are currently considered – type IIb autoimmunity and type I autoallergy[9].

In autoimmune type IIb CSU, mast cells are activated by IgG targeting the high-affinity receptor for IgE on the surface of mast cells (IgG anti-FcεRI) or IgE bound to of mast cells (IgG anti-IgE). Up to 50% of CSU patients have these autoantibodies[10] but their presence is not enough to define autoimmune CSU. According to a task force position paper published in 2013 and later confirmed by the PURIST study, in addition to the presence of IgG autoantibodies by immunoassay, autoimmune CSU requires also a positive BAT and positive autologous serum skin test (ASST)[11,12].

In autoallergic CSU (autoimmunity type I), patients have IgE that recognizes autoantigens, such as thyroperoxidase (TPO), eosinophil peroxidase (EPO), IL-24, double-stranded DNA, tissue factor, FcεRI, and thyroglobulin. For some of these, namely IgE anti-IL-24 and IgE anti-TPO, *in vitro* and even *in vivo* activation of mast cells and/or basophils has been demonstrated[13,14].

The existence of clearly defined and separate auto-IgE and auto-IgG CSU subtypes is still controversial[13]. Recent data suggest that IgG autoantibodies and other autoantibodies (IgE, IgM, and IgA) are co-expressed in the same patient, but actual overlap rates are still unknown[15,16].

The central role of mast cells

Skin mast cells are the primary effector cells in urticaria, regardless of the subtype. Located predominantly in the upper dermis, they are increased in both lesional and non-lesional skin of CSU patients[17]. Detailed knowledge about their activating/inhibitory receptors, signaling pathways, and mediators helps in the identification of new potential treatment targets[13].

Mast cells express several surface activating receptors including FcεRI, Mas-related G protein-coupled receptor PX2 (MRGPRX2), complement receptors (C5aR), protease-activated receptor (PAR)1, PAR2, and cytokine receptors (IL-4Rα and IL-5R), among others[13,18].

Following the interaction of those receptors with their ligands, intracellular signaling is required for mast cell degranulation. Spleen tyrosine kinase and BTK are involved in the signal transduction downstream from FcεRI[19]. Apart from IgE/FcεRI-dependent signaling, IgE-independent pathways have increasingly been studied[20]. Mas-related G protein-coupled receptor X2 (MRGPRX2), for example, is an unselective receptor binding to many different agonists including endogenous neuropeptides (substance P), innate antimicrobial peptides, eosinophil granule proteins, and numerous synthetic drugs, such as codeine, some NSAIDs, and fluorquinolones[21]. Blocking MRGPRX2 seems promising not only for CSU but also for atopic dermatitis (AD), allergic contact dermatitis, non-histaminergic itch, and small molecule compound-induced pseudoallergy[20].

Besides the activating receptors, there are also a few inhibitory receptors on the surface of mast cells, such as sialic acid-binding Ig-like lectin 8 (Siglec 8), which can block mast cell activation upon interaction with their ligands[13].

Inflammation

In CSU, apart from mast cells, eosinophils, neutrophils, lymphocytes, and basophils are found around blood vessels, attracted to the skin in response to chemotactic factors, such as eotaxins, MCP3, RANTES, IL-5, C3a, C5a, TNF, IL-17, and PAF, which are released mainly by mast cells and activated endothelial cells[13].

Basophils have a particularly important role in the pathogenesis of CSU, given the fact that, such as mast cells, they also release histamine, leukotrienes, and cytokines through activation of FcεRI and C5aR[13].

The participation of eosinophils is also noticeable, mainly because of their bidirectional interaction with mast cells. Eosinophil granule proteins can induce mast cell degranulation and mast cell mediators (IL-5, TNF, PAF, and eotaxin) can activate eosinophils[22]. In addition, eosinophils contribute to the activation of the coagulation cascade by expressing tissue factor and they release MRGPRX2 agonists[22].

Serum basopenia and eosinopenia are seen in 10-15% of patients with CSU, probably due to cell migration into the skin, and have been shown to be associated with higher CSU activity, presence of autoantibodies, and poor response to treatment[13,23,24].

Although TH1 cells and TH17 cells are present, TH2 cells are the predominant type of lymphocyte in CSU. They stimulate IgE production and mast cell, basophil and eosinophil activation, by releasing many cytokines, namely IFNγ, TNF, TGFβ, IL-1β, IL-3, IL-4, IL-5, IL-6, IL-13, IL-17, IL-23, IL-24, IL-31, and IL-33[13].

Coagulation cascade

In response to several mediators, eosinophils and dermal endothelial cells express high amounts of tissue factor on their surface, which activate the extrinsic coagulation cascade and leads to the production of activated coagulation factors[13].

Coagulation factors, histamine, bradykinin, PAF, and/or other mediators act on vascular endothelial cells, either directly or through receptors (PAR1), promoting the formation of gaps between endothelial cells therefore increasing vascular permeability and allowing extravasation of plasma that may contain autoanti-bodies to IgE or FcεRI, and/or autoantigens for specific IgE bound to mast cells in the skin[13].

Some activated coagulation factors, such as thrombin and FXa, may also directly induce mast cell activation, by acting on specific mast cell receptors (PAR1 and PAR2, respectively)[13].

In addition, activation of extrinsic coagulation and fibrinolysis promotes the formation of complement components (C5a and C5b and/or C3a and C3b) that further activate mast cells and basophils, since both these cells express complement receptors (C3aR and C5aR) on their surface[13]. However, this hypercoagulative state in CSU is regarded mostly as a local process accompanied by active fibrinolysis without increased risk for thrombotic events[25]. Nevertheless, they may be related to the elevation of serum D-dimers[26], which along with other serum biomarkers may be increased in CSU patients, namely interleukin-6[27], interleukin-17[28], and C-reactive protein (CRP)[29], whose levels apparently correlate with CSU activity. Furthermore, the proposed association between increased CRP, D-dimer levels, IL-6, C3, C4, ASST positivity, and CSU activity may reflect the complexity of this disease[29], suggesting that autoimmunity, inflammation, complement activation, and coagulation are all somehow connected and continuously contributing for the maintenance and/or exacerbation of urticaria[13].

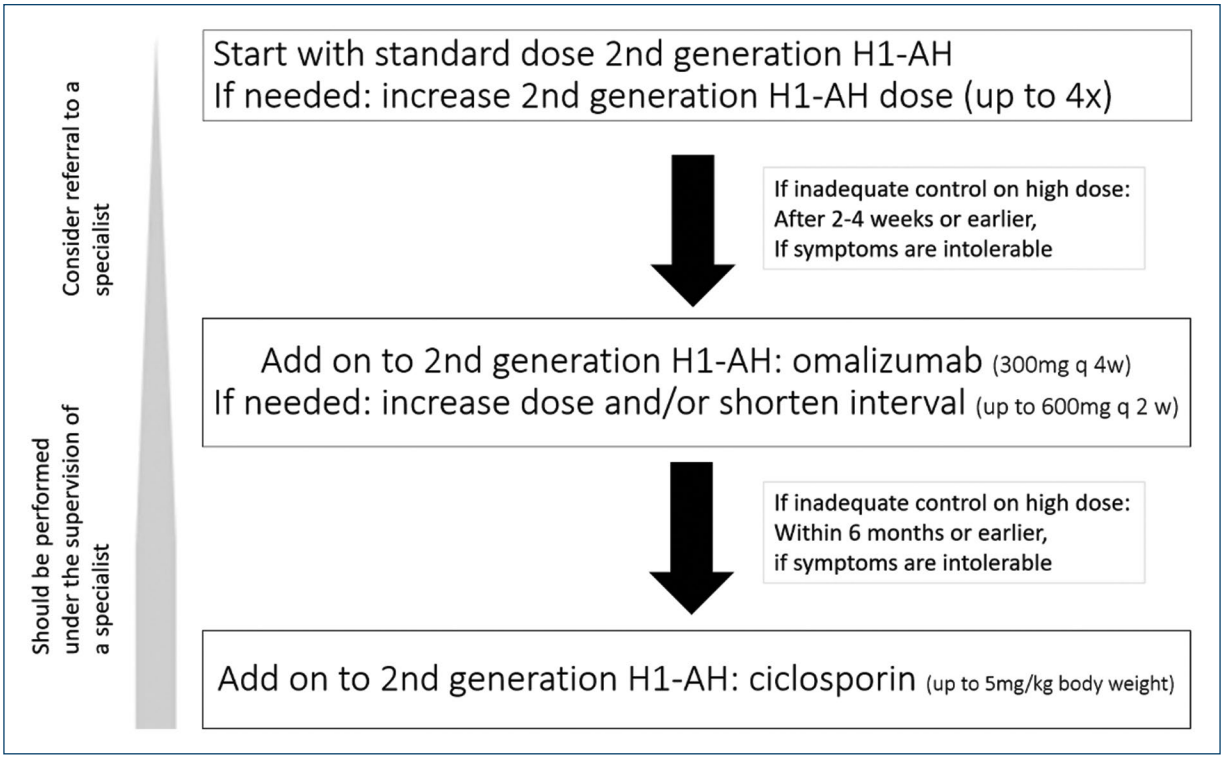

Figure 1. Current algorithm for CSU treatment according to the international EAACI/GA²LEN/EuroGuiDerm/APAAACI recommendations. Of note: in addition, a short course of glucocorticosteroids may be considered.

Current management guidelines for CSU

Current treatment options proposed within the international EAACI/GA²LEN/EuroGuiDerm/APAAACI recommendations for the management of CSU (Fig. 1) are mainly symptomatic with the overall goal to "treat the disease until it is gone," aiming at complete symptom control (UAS7 = 0 and/or UCT = 16) and a normalization of quality of life[8].

In addition to general measures, namely elimination of underlying causes and avoiding triggers such as stress or NSAIDs, recommended pharmacological therapy includes H1-antihistamines (H1-AH), OMA, and immunosuppressants, namely ciclosporin (CsA).

H1-antihistamines

H1-antihistamines have been recommended for the treatment of urticaria for more than 70 years[7]. They combine with and stabilize the inactive form of the H1 receptor, acting as inverse agonists and not as antagonists[3,8].

First-generation H1-AH is strongly discouraged both in urticaria and other allergic disorders, because of their side effects (e.g., anticholinergic and sedative) and multiple drug interactions[8,30]. Non-sedating 2nd-generation H1-AH has a good safety profile, even at higher doses and after many years of continuous use, and is widely accepted as the first-line option for the management of CSU. They should be started in the standard dose and taken daily rather than on demand[8]. More than half of CSU patients cannot completely control their symptoms with standard doses[6]. According to several studies showing additional benefits of updosing 2nd-generation H1-AH in urticaria[6,31], in patients with insufficient response, these drugs should have the dose increased up to fourfold before alternative treatments are considered[8]. Updosing is favored over mixing different 2nd-generation of H1-AH. Patients must be aware that 2nd-generation H1-AH updosing is off-label and higher than fourfold has not been tested therefore is not recommended[8].

There are still no well-designed clinical trials comparing the effectiveness and safety of the different 2nd-generation H1-AH in urticaria, then so no suggestion can be made regarding which one to choose[8].

In addition to updosing 2nd-generation H1-AH, the American guidelines for the management of urticaria also propose combining other therapies, such as H2-antihistamines, leukotriene receptor antagonists, or even a 1st-generation H1-AH at bedtime[32].

Those recommendations are mostly based on small case series and expert opinion and are not included within the main recommendation in the international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline[8].

Omalizumab

OMA is a humanized anti-IgE mAb, which selectively binds and lowers free IgE, consequently decreasing FcεRI on basophils and mast cells due to the internalization and degradation of unattached FcεRI[33,34]. Reduced FcεRI expression seems to increase cells' resistance to IgE and IgG anti-FcεRI activation and therefore reduce histamine production and inflammation[34].

Approved since 2014 for CSU in patients ≥ 12 years of age, OMA is still the only biological drug licensed for the treatment of CSU to date and is recommended as an add-on treatment after failure of antihistamine therapy at maximum doses[13].

For the last decade, OMA has proven its efficacy and safety in both clinical trials and real-life studies[35,36].

A recent meta-analysis of 67 real-world studies presented an average 25.6-point improvement in UAS-7 with OMA treatment (vs. a 14.9-22.1-point improvement reported in clinical trials). The same study reported a complete response rate of 72.2% and an additional partial response rate of 17.8%, as well as an average adverse event rate of 4.0% (vs. 2.9%-8.0% reported in clinical trials)[37].

These data suggest that the efficacy of OMA in real-life practice may exceed what was previously reported in clinical trials, with a safety profile similar to or even better than the one observed during clinical trials[37].

The benefits of OMA include not only the prevention of wheals and angioedema[38] but also a remarkable increase in patients' quality of life[39] and maintenance of efficacy in case of a relapse after suspension[40].

In CSU, OMA should be started with subcutaneous injections of 300 mg every 4 weeks[8]. In patients who do not respond completely, OMA may be used in higher doses, shorter intervals, or both (up to 600 mg every 2 weeks)[41-43], but patients must be warned that OMA updosing is off-label[8]. There are no definitive biomarkers to predict and explain why some patients have their symptoms controlled after the first injection whereas others take up to 6 months to respond[44]. Poor and/or slower response to OMA has been associated with type IIb autoimmunity[45] and consequently, features of this specific CSU subtype – positive BAT/ASST[44], low total IgE levels[13,44], and basopenia/eosinopenia – have been postulated as possible predictors of a negative or slow response to OMA. Fast response is usually observed in patients with high serum IgE or when IgE increases after the first OMA injections[46].

Most responders need long treatment periods until CSU remission, often more than 4-5 years, but it is hard to predict the right moment to discontinue OMA treatment and how to stop, either abruptly or progressively, increasing intervals between administrations until 6-8 symptom-free intervals. In case of a relapse after withdrawal, OMA has the same efficacy when re-initiated.

Ciclosporin

CsA is used off-label in CSU, in doses between 3 and 5 mg/kg/day, as a third-line treatment for patients without sufficient benefit from any dose of antihistamine and OMA in combination[8].

CsA is an immunosuppressive drug which inhibits mast cell and basophil mediator release[45]. Its effectiveness in CSU has been demonstrated by several studies[47-49] with response rates up to 73% in a recent meta-analysis[48].

Predictors of favorable response to CSA have been explored and an association between type IIb phenotype and good/faster response to CSA has been proposed[50,51]. This means that patients with low IgE levels[52] or positive BAT[50] presumably have good responses to this drug, although, in a recent systematic review, no biomarker was consistent enough to be recommended[49].

In addition in patients with this type IIb subtype of CSU, short courses of CSA have been shown to induce prolonged remissions in patients with CSU, without needing additional treatment[53].

There are some concerns around the wider administration of this drug due to its poor safety profile, namely the risk of hypertension and cumulative renal impairment[49].

Additional treatment options

In antihistamine refractory patients, the previously presented stepwise approach should be followed. However, guidelines and experts recognize that OMZ has limitations due to its high price and CSA may not be suitable because of adverse effects[8]. Therefore, in some cases, alternative treatments are needed.

Systemic corticosteroids (20 and 50 mg/d of prednisone equivalent) may be used in short courses (to a maximum of 10 days) and only for acute exacerbations of CSU, not in the long term[8].

Other treatment options for CSU include dapsone, colchicine, sulfasalazine, hydroxychloroquine, methotrexate, tricyclic antidepressants, interferon, plasmapheresis,

phototherapy, and intravenous Ig. These might be used in individual cases, but overall evidence to support their selection is weak[13].

Therapies in development for CSU

Table 1 summarizes potential targets and agents under investigation for the treatment of CSU in adult patients.

Biologicals

Ligelizumab

Ligelizumab (QGE031), a new generation humanized anti-IgE mAb, demonstrated a 40-fold to 50-fold greater affinity to IgE as compared with OMA[53]. Preliminary results of a phase IIb trial demonstrated rapid onset of action, dose-dependent efficacy, and superiority to OMA in refractory CSU patients[54], but unfortunately, this was not confirmed by the following studies.

In PEARL-1 and PEARL-2 (NCT03580369 and NCT03580356), a phase III, replicate, multi-center, randomized, double-blind, parallel-group studies, which enrolled over 2000 patients aged 12 years or older with CSU refractory to H1-AH56, the primary endpoint was met (change from baseline in Urticaria Activity Score [UAS7] at week 12) but with no superior efficacy versus OMA. A good safety profile, consistent with previous studies, was reported[55]. Therefore, Novartis has stopped the development of ligelizumab for CSU.

UB-221

UB-221 is a recombinant humanized anti-IgE mAb distinct from OMA and ligelizumab since it neutralizes both soluble IgE and CD23-bound IgE[56]. A phase I study (NCT03632291) with a single UB-221 administration to patients with CSU has presented significant symptom relief along with a fast decrease in serum free-IgE level. Further phase I and phase II studies are being conducted to assess the efficacy, safety pharmacodynamics, and pharmacokinetics of this emerging intravenous drug[56].

Dupilumab

Dupilumab is a recombinant human IgG4 mAb that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit of the IL-4/IL-13 receptor. It is currently approved for asthma, AD, chronic rhinosinusitis with nasal polyposis (CRSwNP), prurigo nodularis, and eosinophilic esophagitis (EoE)[57].

Given the known predominance of type 2 inflammation in CSU, with IL-4 and IL-13 likely contributing to the inflammatory response through their effects on T-cell differentiation and IgE class switching, dupilumab has been postulated as a possible effective treatment in chronic urticaria[58].

In fact, several case reports have shown efficacy in H1-AH and OMA-refractory CSU[58], some with sustained benefits many months after suspension, suggesting a potential disease-modifying effect of dupilumab in CSU[59].

The randomized, placebo-controlled, phase 3 clinical trial LIBERTY-CSU CUPID (NCT04180488) in H1-AH resistant CSU (study A and C: OMA naive; study B: OMA intolerant or incomplete responders)[60] showed a clinically meaningful improvement in itch, hive severity, and urticaria activity at week 24, regardless of prior history of allergic rhinitis, asthma, AD, and normal and elevated IgE serum levels[61]. Nevertheless, contrary to positive results in OMA-naive patients (study A), dupilumab did not meet primary endpoints in patients who had failed OMA (study B), and the trial was stopped due to futility[61].

Still, dupilumab seems to be a possible alternative treatment in biologic-naive H1-AH refractory patients and is currently being reviewed by FDA for that indication[60].

Secukinumab

Secukinumab is an anti-IL-17 mAb, widely used in moderate-to-severe plaque psoriasis, psoriatic arthritis, axial spondyloarthritis, and juvenile idiopathic arthritis.

As high serum and skin levels of IL-17 have been found in CSU, supposedly associated with high activity[62], the role of IL-17 role in CSU pathogenesis has been suggested.

A recent study described the successful treatment of eight H1-AH and OMZ refractory CSU patients with secukinumab 150 mg once a week for 4 consecutive weeks followed by 150 mg every 2 weeks, although with a slow onset of action[63]. Future studies with larger numbers of patients are needed to confirm these results.

Tezepelumab

Tezepelumab is a first-in-class human IgG2λ mAb against the action of TSLP. It is the only biological currently approved by FDA and EMA for severe asthma, and other indications, such as CRSwNP, EoE, and CSU, are under investigation[64].

Table 1. Potential targets and agents under investigation for the treatment of CSU in adult patients

Target	Drug	Other names	Manufacturer	Trial phase	Trial identifier/designation	Status
IgE	Ligelizumab	QGE031	Novartis	III	PEARL-1 PEARL-2	Completed
	UB-221		United BioPharma	II	NCT05298215	Recruiting
				I	NCT04175704	Not yet recruiting
				I	NCT04404023	Not yet recruiting
				I	NCT03632291	Completed
IL-4/IL-13	Dupilumab	REGN668/ SAR231893	Sanofi	III	NCT04180488 (LIBERTY-CSU CUPID)	Recruiting
TSLP	Tezepelumab		Amgen	II	NCT04833855 (INCEPTION)	Completed
IL-5	Mepolizumab		GlaxoSmithKline	I	NCT03494881	Recruiting
IL-5Rα	Benralizumab		AstraZeneca	IV II	NCT03183024 NCT04612725 (ARROYO)	Completed
Siglec 8	Lirentelimab	AK002	Allakos	IIa	NCT03436797 (CURSIG)	Completed
				IIb	NCT05528861 (MAVERICK)	Recruiting
KIT	Barzolvolimab	CDX-0159	Celldex Therapeutics	Ib	NCT04538794	Completed
				II	NCT05368285	Recruiting
BTK	Fenebrutinib	GDC-0853	Genentech	II	NCT03137069	Completed
				II	NCT03693625	Terminated*
	Remibrutinib	LOU064	Novartis	IIb	NCT03926611	Completed
				III	NCT05513001	Recruiting
				III	NCT05030311 (REMIX-1)/ NCT05032157 (REMIX-2)	Active, not recruiting
				III	NCT05048342 (BISCUIT)	Active, not recruiting
				III	NCT05795153	Recruiting
	Rilzabrutinib	PRN1008/ SAR444671	Sanofi	II	NCT05107115 (RILECSU)	Active, not recruiting

*Recruitment was stopped after an interim analysis of the parent GS39684 study.

TSLP is an epithelial cell-derived cytokine that acts as an alarmin, promoting inflammation through the stimulation of dendritic cells, mast cells, and type 2 innate lymphoid cells[62].

As increased TSLP expression has been demonstrated in the lesional skin of CSU patients and tezepelumab has proven to cause sustained decreases in circulating eosinophils and total serum IgE[62], it has been postulated that this drug could be a useful alternative therapy for patients with H1-AH and OMA refractory CSU.

A 183-patient phase IIb trial to evaluate the efficacy and safety of tezepelumab in adults with CSU (INCEPTION; NCT04833855) has been recently completed[65].

Mepolizumab and other anti-IL-5 mAbs

Mepolizumab is a humanized mAb against IL-5, the key cytokine for the activation and survival of eosinophils, which is approved for the treatment of serious eosinophilic asthma, CRSwNP, hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis[66].

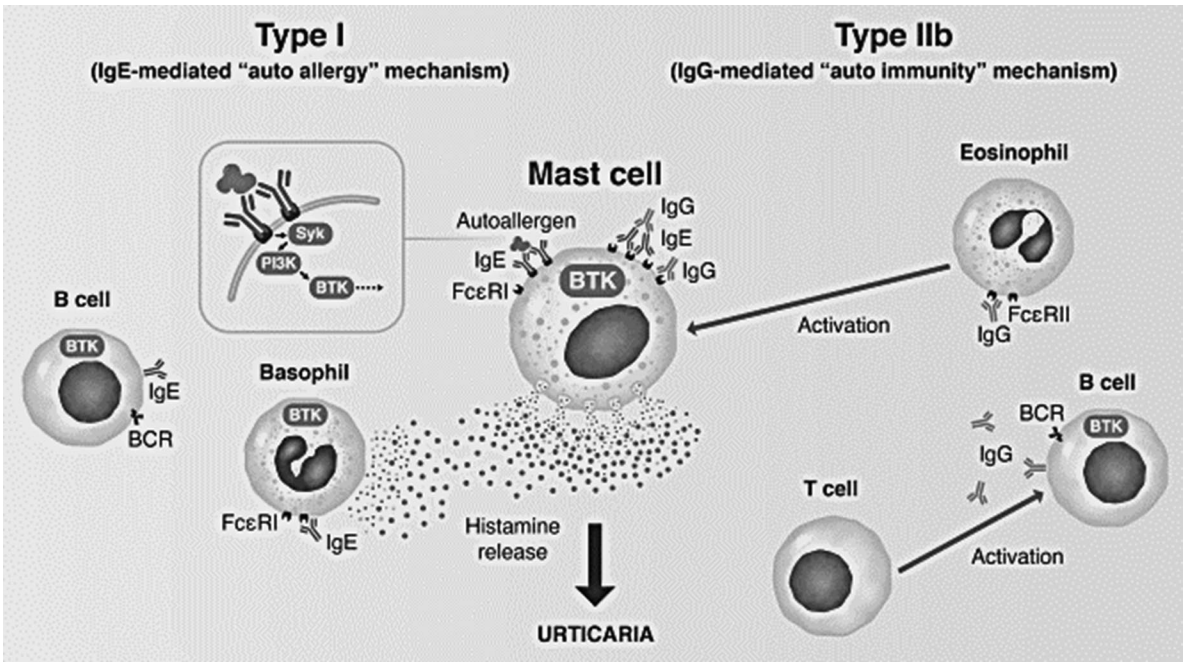

Figure 2. The role of BTK as an intracytoplasmic mediator of both type I and type IIb subtypes of CSU
(adapted from: Mendes-Bastos P, Brasileiro A, Kolkhir P, et al. Bruton's tyrosine kinase inhibition – An emerging therapeutic strategy in immune-mediated dermatological conditions. Allergy. 2022;77:2355-2366).

Considering the role of eosinophils in CSU, mepolizumab has been hypothesized as a valid option for the treatment of CSU[67].

In 2018, Magerl et al. reported the case of a patient simultaneously affected by severe refractory eosinophilic asthma and CSU treated with mepolizumab, who showed good control of urticarial symptoms since the first administration[68].

There is an ongoing interventional, single-arm, open-label, phase I clinical trial to evaluate the efficacy of mepolizumab in the treatment of CSU[69].

Reslizumab, another anti-IL-5 biological approved only for severe eosinophilic asthma, has shown good efficacy in a single patient with severe asthma, CSU, and cold urticaria[70]. However, no further studies have been published.

Benralizumab, a murine mAb that binds to the isoleucine-61 of the domain 1 of human IL-5Rα, is licensed and used for severe eosinophilic asthma, but since it depletes eosinophils and basophils from affected skin, it may also improve symptoms of CSU[67].

In phase IV, non-randomized, single-center trial (NCT03183024) with a total of 12 patients, CSU patients unresponsive to H1-AH treated with a single dose of subcutaneous placebo followed by 3 monthly subcutaneous benralizumab 30 mg injections had sustained mean changes in the UAS7 from baseline to week 20[71].

Furthermore, a phase IIb multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial (ARROYO; NCT04612725) to investigate the efficacy of benralizumab in H1-AH refractory CSU[72].

Lirentelimab

Siglecs (sialic acid Ig-like lectins) are I-type transmembrane proteins of the Ig superfamily found primarily on the surface of immune cells and are involved in inhibitory cell signaling. Siglec-8 is uniquely expressed on eosinophils, mast cells, and basophils and has been studied as a potential therapeutical target in CSU as well as in other types of chronic urticaria[3].

Studies in mice have shown that monoclonal antibodies binding to Siglec-8, namely lirentelimab (AK002), inhibited MC degranulation, and cytokine production and induced eosinophil apoptosis[73].

Results from a phase IIa trial (CURSIG; NCT03436797) reinforce that lirentelimab reduces disease activity in CSU patients, including those previously treated with anti-IgE therapy[74]. In this study, patients received 6 monthly intravenous infusions of lirentelimab and were followed for

another 8 weeks. Both OMA-naive and OMA-refractory patients had a significant decrease in disease activity at week 22 (mean UAS7 change: –73% and –57%, respectively) without treatment-related serious adverse events[74].

A phase IIb study to assess subcutaneous lirentelimab in patients with CSU is currently recruiting (MAVERICK, NCT05528861)[75].

Barzolvolimab

Barzolvolimab (CDX-0159) is a humanized mAb developed to specifically inhibit the activation of KIT receptors by stem cell factor (SCF), which is essential for mast cell differentiation, proliferation, and survival[76].

This drug was initially studied in chronic inducible urticaria, reaching 95% of complete responses in H1-AH resistant patients after a single 3 mg/kg intravenous administration. Tryptase suppression, skin mast cell ablation, and increased SCF were observed in accordance with the noticeable efficacy of the drug[77].

A phase Ib trial (NCT04538794) with 45 patients to determine the safety of different doses of barzolvolimab in CSU showed rapid and lasting responses across multiple dosing groups (1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg), with 56% of all patients experiencing complete responses at week 12, regardless of previous treatment with OMA[77].

Multiple administrations of barzolvolimab demonstrated a favorable safety profile, consistent with single-dose studies, with mostly mild or moderate adverse events (hair color changes, COVID-19, headache, neutropenia, and urinary tract infections) with no need for drug withdrawal[77].

The ongoing phase II clinical trial (NCT05368285) will provide further information on the therapeutic potential of barzolvolimab in CSU patients including those with prior biologic therapy.

Small molecules

MRGPRX2 antagonist

MRGPRX2 is a multiligand receptor, which promotes non-IgE driven mast cell degranulation, as well as neurogenic and eosinophilic inflammation[78].

MRGPRX2-positive mast cells and some of their ligands (including substance P) are upregulated in the blood and/or skin of patients with pruritic skin diseases such as CSU or AD[78], so it has been proposed as a promising therapeutical target for these conditions.

A preliminary study showed that EP262, a potent MRGPRX2 antagonist, can inhibit mast cell degranulation, both *in vitro* and *in vivo*[79]. This novel IgE-independent mechanism of action, with the potential for once-daily oral administration and a safety profile that is devoid of side effects, seems promising. A phase I first-in-human study will be initiated by Escient Pharmaceuticals to evaluate the safety, tolerability, and pharmacokinetics of the drug in healthy volunteers[80].

BTK inhibitors

BTK, a non-receptor (cytoplasmic) tyrosine kinase, is involved in several immunological pathways, including signaling through Fcε receptors but also through B-cell receptors, toll-like receptors, chemokine receptors, and CD40[81].

BTK has a particularly important role in B-cell development and activation, which has motivated the development and approval of BTK inhibitors (namely ibrutinib) to treat B-cell malignancies[81].

More recently, BTK has been found in many other non-B cells, such as mast cells, basophils, monocytes, and neutrophils, participating in several immunological pathways and the pathophysiologic mechanisms of inflammatory, autoimmune, and allergic diseases[3,81].

In CSU, BTK is a key intracytoplasmic mediator of both type I and type IIb subtypes of CSU, not only because it is involved in mast cell degranulation but also because it mediates autoantibody production by B cells (Fig. 2). Interestingly, BTK has been proposed as particularly helpful in the more "treatment-resistant" type IIb CSU[81].

Fenebrutinib

A recent double-blind, placebo-controlled, phase II study (NCT03137069) enrolled 93 participants to evaluate the efficacy, safety, and pharmacokinetics of the oral selective BTK inhibitor fenebrutinib for 8 weeks compared with placebo in H1-AH refractory CSU[82].

Fenebrutinib 200 mg twice daily and 150 mg daily, but not at 50 mg daily, showed dose-dependent improvements in UAS7, especially in those patients with type IIb autoimmunity, but reversible grade 2 and 3 liver transaminase elevations occurred with these higher doses[82].

Remibrutinib

Remibrutinib, a highly selective, oral BTK inhibitor has been lately explored as a novel option for the treatment of CSU, obtaining promising results.

A randomized, double-blind, placebo-controlled phase IIb trial (NCT03926611), completed in 2022, evaluated the efficacy and safety of remibrutinib administered for 12 weeks in patients with CSU inadequately controlled with H1-AH, with or without prior exposition to OMA. Patients were randomized to one of six doses of remibrutinib – 10 mg i.d, 35 mg i.d, 100 mg i.d, 10 mg b.i.d, 25 mg b.i.d, or 100 mg b.i.d – or placebo, and at week 4 and week 12 all doses demonstrated superiority, with a rapid onset of action and independent of previous treatment with anti-IgE mAb and patients' baseline IgE[83].

The median time to complete urticaria control (UAS7 = 0) was shortest with remibrutinib 25 mg b.i.d, which may be at least partially explained by the short half-life of the drug[83].

Moreover, remibrutinib showed a favorable safety profile, with mostly mild or moderate adverse events and no apparent dose-dependent pattern[83]. Several phase III trials with this drug are currently in progress.

Rilzabrutinib

Rilzabrutinib (PRN1008/SAR444671) is another oral small molecule inhibiting BTK which is currently under investigation for several conditions, including H1-AH refractory CSU. A phase II trial assessing the safety and effectiveness of rilzabrutinib in three different doses compared with placebo is ongoing and due to be concluded in 2024[84].

Conclusion

New therapies for CSU are urgently needed, given the high percentage of patients who respond poorly or not at all to currently available treatments.

This review summarizes the current treatment protocol for treating patients with CSU, as well as present novel drugs under investigation in clinical trials for this condition. Several promising therapeutic targets have been identified and individualized tailored therapies, based on the endotype and phenotype of each CSU patient, should be the future.

Several drugs are expected to be available in the next few years as add-on or alternative therapies for symptomatic control in patients who are resistant to H1-AH and OMA. A bigger ambition is the development of preventive or curative treatments, which may arise with the expanding comprehension of CSU pathogenesis.

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Conflicts of interest

M. Gonçalo has received fees for lectures and/or been an advisor for Abbvie, Astra-Zeneca, Leo Pharma, Lilly, Novartis, Pfizer, Sanofi, Takeda. The other authors declare no conflicts.

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. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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

Epidemiological profile of patients with chronic lower extremity ulcers in two public hospitals in southern Brazil

Perfil epidemiológico de pacientes com úlceras crônicas do membro inferior em dois hospitais públicos no sul do Brasil

Breno S. Kliemann[1,2a], Victoria M.R. Pagliosa[3b], Jorge E.F. Matias[3,4c], Antonio C.L. Campos[3,4d], and Adriano A. Mehl[1e]*

[1]Department of Dermatology, Hospital Santa Casa de Curitiba, Curitiba; [2]Hospital de Dermatologia Sanitária do Paraná, Piraquara; [3]Department of Surgical Clinical Care, Universidade Federal do Paraná, Curitiba; [4]Departament of Surgery, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba. Paraná, Brasil

ORCID: [a]0000-0002-2843-3196; [b]0009-0005-6643-0075; [c]0000-0001-6377-8870; [d]0000-0001-5080-8380; [e]0000-0003-1769-3897

Abstract

Objective: The objective of this study was to typify the clinical and epidemiologic profile of outpatients with chronic lower extremity ulcers in two reference centers of the public health system in Paraná state, in Southern Brazil. **Methods:** Demographic, clinical, and anthropometric data about the patients were collected at each assessment, as well as information on the etiology, size, and duration of ulcers. **Results:** There were 68 study participants, 40 (58.82%) men and 28 (41.18%) women, with an average age of 65.1 (± 13.6) years and an average 1.6 ulcers per patient. The average duration of ulcers was 9.7 (± 12.2) years, and the average size of the largest lesion of each patient was 80.0 (± 140.0) cm². Regarding body mass index, 19 (27.94%) patients were eutrophic, 21 (30.88%) were overweight, 23 (33.82%) were obese and 5 (7.35%) were underweight. The most common etiology was venous ulcers, present in 39 (57.35%) patients. **Conclusion:** The clinical and epidemiologic profile of patients is similar to that in developed nations. There was a longer time since onset and a larger average size of ulcers than described in the medical literature.

Keywords: Skin ulcer. Leg ulcer. Foot ulcer. Wound healing. Wounds.

Resumo

Objetivo: Caracterizar o perfil clínico e epidemiológico de pacientes ambulatoriais com úlceras crônicas de membros inferiores atendidos em dois hospitais de referência do sistema público de saúde no estado do Paraná, na Região Sul do Brasil. **Métodos:** Em cada avaliação, foram coletados dados demográficos, clínicos e medidas antropométricas dos pacientes, além de informações sobre a etiologia, tamanho e tempo de evolução das úlceras. **Resultados:** Participaram 68 pacientes, 40 (58,82%) homens e 28 (41,18%) mulheres, com idade média de 65,1 (± 13,6) anos e com a média de 1,6 úlceras por paciente. O tempo médio de evolução das úlceras foi de 9,7 (± 12,2) anos, e o tamanho da maior ferida de cada paciente era em média 80,0 (± 140,0) cm². Considerando o índice de massa corporal, 19 (27,94%) pacientes eram eutróficos, 21 (30,88%) tinham sobrepeso, 23 (33,82%) tinham obesidade e 5 (7,35%) tinham magreza. A principal etiologia das úlceras

***Correspondence:**
Breno S. Kliemann
E-mail: brenokliemann@gmail.com

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crônicas de membros inferiores foi a venosa, presente em 39 (57,35%) pacientes. **Conclusões:** O perfil clínico e epidemiológico dos pacientes é semelhante ao de países desenvolvidos. O tempo de evolução e o tamanho médio das lesões foram maiores do que os descritos na literatura.

Palavras-chave: Úlcera cutânea. Úlcera da perna. Úlcera do pé. Cicatrização. Ferimentos.

Introduction

Skin ulcers are a highly prevalent health issue, mostly in elderly patients, and lead to healthcare costs estimated in over 20 billion dollars per year in the United States[1]. They are characterized by loss of continuity affecting epidermis and dermis, which may also affect deeper tissues, such as subcutaneous, fascia, muscles, and tendons and may expose blood vessels, bones, and joints. On an acute loss of continuity, there is a stimulus for the beginning of the healing process, which is divided in three phases: inflammatory, proliferative, and remodeling. If, however, there is interference in the physiologic healing process – especially during the inflammatory phase – the lesion will become a chronic one. Chronic ulcers are those with no signs of healing stimulus after at least 4 weeks, persisting stationed within the inflammatory phase of healing[2,3].

A chronic ulcer brings significant morbidity and may affect in many ways the patient's quality of life, in aspects ranging from malodor, exudate draining, need for frequent dressing changes, and compromised mobility, to the increase in the number of hospital admissions up to the need for amputation[4,5]. It also brings an increase in mortality rate, usually due to secondary infections with subsequent systemic involvement. For instance, diabetic ulcers have a mortality rate in 5 years of up to 30.5%[3,6,7], similar to the one found in cancer (31%)[8].

Factors that may negatively affect the healing of a skin ulcer, leading to chronification, can be divided between local and systemic factors. Among local factors are tissue oxygenation, infection or critical colonization of the wound, biofilm formation, and the possibility of infection in adjoining tissues. Several systemic factors are reported to influence in the healing process: sustained hyperglycemia in diabetes mellitus (DM), for instance, which delays healing by increasing reactive oxygen species and advanced glycation end products, besides causing angiopathic and neuropathic complications[9,10]. Obesity also dysregulates the systemic inflammatory response, increasing the risk of healing complications. Alcoholism may impair the proliferative phase of healing by reducing angiogenesis. Smoking leads to tissue hypoxia due to toxic effects of nicotine, carbon monoxide, and hydrogen cyanide, among other mechanisms. Some drugs also negatively affect healing. For instance, glucocorticoids may harm fibroblast proliferation and the cell defense response, augmenting the risks of local infection. Non-steroidal anti-inflammatory drugs decrease angiogenesis, and chemotherapic drugs hinder cell proliferation[11].

Nutrition is another very important factor for a healthy healing. Proteins are essential to collagen production, angiogenesis, and tissue regeneration, and a hyperproteic diet may be indicated[12]. Supplementation of amino acids such as arginine and glutamine may benefit healing[13,14]. Adequate intake of fluids, calories, fatty acids, vitamins, and micronutrients such as magnesium and zinc is also of utmost importance for healing. Protein-caloric malnutrition is, therefore, a frequent and underdiagnosed cause of non-progression in wound healing[14,15].

The lower extremity (LE) is the most frequent site of a chronic ulcer – especially in the distal portions of the leg and in the foot. In developed countries, the most common etiology of a chronic lower-extremity ulcer (CLEU) is chronic venous insufficiency (CVU), which comprises up to 80% of cases. Peripheral artery disease, either isolated or in association to CVU, is present in up to 25% of CLEU located in legs[16]. Non-controlled systemic arterial hypertension (SAH) and inflammatory diseases such as pyoderma gangrenosum are among other less frequent causes[17,18]. Foot ulcers are usually related to some degree of neuropathy (autonomic, sensitive, or motor), with consequential impairment of protective mechanisms of skin barrier, and biomechanical alterations in gait, leading to repeated traumas and smaller regenerative capacity. In developed countries, this neuropathy is most commonly associated to DM[16]. Pressure injuries are another frequent cause of skin ulcers in inpatients and those with impaired mobility[12].

Although there are many studies regarding the clinical and epidemiological profile of patients with CLEU, most of them come from developed countries, mainly in Europe and North America. These countries have already been through the epidemiologic transition, when improved life conditions resulted in decreased morbimortality by transmittable diseases, but with an

Table 1. Clinic and nutritional characteristics of CLEU patients

Variable	Mean ± standard deviation	Median (minimum-maximum)
Age (years)	65.1 ± 13.6	66 (16-91)
BMI (kg/m²)	28 ± 6.4	27.8 (13.7-45.9)
Duration (years)	9.7 ± 12.2	5.5 (0.12-50)
Number of wounds	1.6 ± 0.98	1 (1-5)
Size of larger wound (cm²)	80 ± 140	30 (0.25-900)

CLEU: chronic lower extremity ulcers; BMI: body mass index.

elevation in the rate of degenerative chronic diseases, due to enhanced life expectancy. This scenario may vary considerably in other regions of the world. Besides that, socioeconomic status of the individual and of the population seems to also affect healing[4]. In the least developed or developing countries, the main causes of CLEU are infectious and neoplastic[19,20]. There are few studies about the clinical and epidemiological profile of CLEU patients in Brazil, a country characterized by a double burden of diseases: while better life expectancy has led to an increase in chronic diseases such as DM and vascular disease, there is still a high prevalence of infectious diseases and of food insecurity resulting in malnutrition[21-24]. Public health problems unfortunately keep Brazil as the second country in the world regarding the number of leprosy cases, a disease which is a common cause of peripheral neuropathy and that may contribute to development of ulcers[25].

The objective of this study is to characterize the clinical and epidemiological profile of outpatients with CLEU, treated in two reference hospitals of the public health system in the state of Paraná, in the Southern region of Brazil, and to search for factors that may be related to the severity of these ulcers.

Methods

This is an analytic and cross-sectional study, which evaluated 68 patients with CLEU, totaling 109 lesions, in public health-care outpatient clinics of two tertiary hospitals in the Brazilian state of Paraná: Hospital Santa Casa de Curitiba, in the city of Curitiba, and Hospital de Dermatologia Sanitária do Paraná, in the city of Piraquara (a city in Curitiba metropolitan area).

Patients older than 18 years having LE ulcers for more than 4 weeks, presenting for medical visit or for dressing changes in the participating clinics, were invited to take part in the study, and data collection was performed during the period of June 2021-February 2022.

During the initial assessment, data were collected on demographic (age, sex, and municipality of residence) and clinical (including information on comorbidities, drugs used, and risk factors such as smoking and alcoholism) characteristics. Anthropometric measures of height and weight were also performed, to allow calculation of body mass index (BMI). In regard to BMI, patients were classified in groups of nutritional status according to the World Health Organization (WHO) cut offs: grades 1-3 underweight, normal weight, overweight, or grades 1-3 obesity.

In relation to CLEU, data were collected on etiology (as assessed by attending physicians and registered in medical records), characterizing as venous, arterial, diabetic, neuropathic ulcer of leprosy, pressure injury, or post-traumatic. It was also noted presence or absence of lymphoedema as an etiologic factor.

Considering the number of lesions, patients were divided in three groups: those with one, two or with three or more wounds. Wounds were divided according to their anatomic location, as proposed by Baker et al.[26], as located in proximal LE (that is, located in the larger calf circumference or proximal to it), in distal leg, or in the foot. Moreover, duration (in years since the onset of ulcer) and size (calculated by multiplying the largest longitudinal and transverse axes of each ulcer) were noted. The size was measured and registered with validated, sterilizable, and flexible rulers[2], during dressing changes.

Data were stored in Microsoft Office Excel® (2019 version). Results of quantitative variables were described by mean, standard deviation, median, minimum, and maximum. Categorical variables were described by absolute and percentage frequencies.

Besides the descriptive analysis, it was verified if duration, size, or number of CLEU per patient would

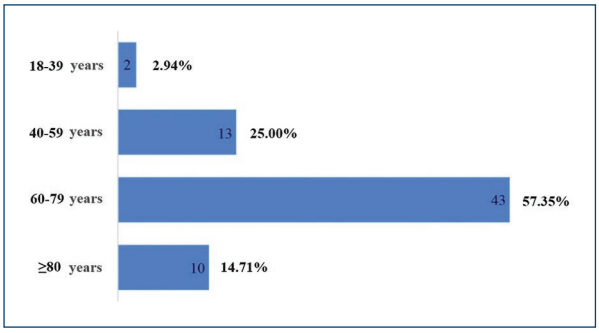

Figure 1. Distribution of CLEU patients according to age group. CLEU: chronic lower extremity ulcers.

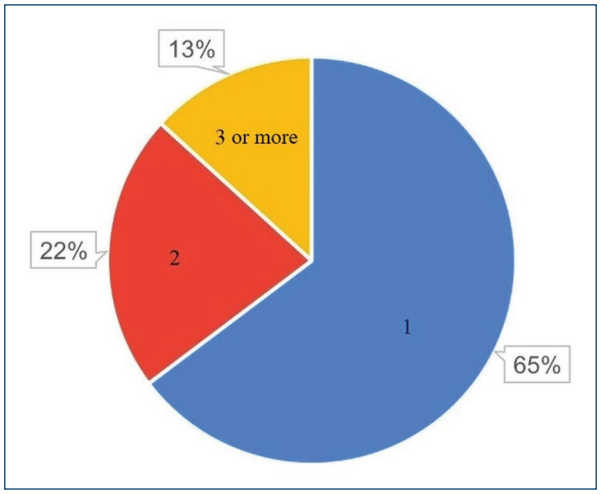

Figure 2. Number of CLEU per patient. CLEU: chronic lower extremity ulcers.

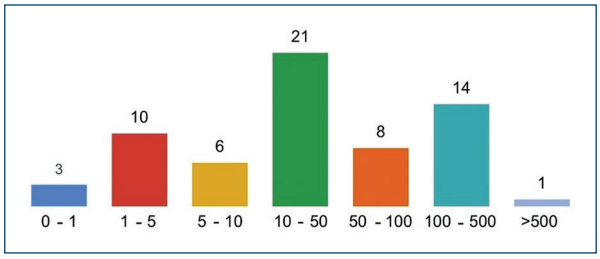

Figure 3. Distribution of CLEU patients according to size of larger wound, in cm². CLEU: chronic lower extremity ulcers.

potentially be related to any aforementioned variable. To assess the association between two categorical variables, the Pearson's Chi-squared test was performed. To compare the duration of wound among groups defined by classification of categorical variables, nonparametric Mann-Whitney or Kruskal-Wallis tests were performed. To compare groups defined by the number of lesions (with one, two, or at least three wounds) in relation to quantitative variables, the analysis of variance model or nonparametric Kruskal-Wallis test was performed. To analyze the correlation between two quantitative variables, Spearman correlation coefficients were estimated. Normality assumption of continuous quantitative variables was performed by Kolmogorov-Smirnov test. Values of $p < 0.05$ indicated statistical significance. Data were organized in an Excel® sheet and analyzed with IBM SPSS Statistics software (v.20.0. Armonk, NY: IBM Corp).

Approval for the study was granted by the Ethics in Research Committee of Federal University of Paraná (CAAE 44216921.8.0000.0102, approval number 4.649.628). Both participating hospitals also provided consent to performing the research in their outpatient clinics. An informed consent term was provided for all participant patients to sign.

Results

A total of 68 patients took part in the study: 40 (58.82%) and 28 (41.18%) females. As patients presented a mean number of 1.6 CLEU each, a total of 109 wounds were recorded. Further data on age, BMI, duration of ulcer, number of wounds per patient, and size of largest wound are presented in table 1. The most common age group was 60-79 years old (Fig. 1), corresponding to 43 (57.35%) patients. Forty-three (63.24%) patients presented with only one CLEU (Fig. 2). Only 1 (1.59%) patient had a CLEU larger than 500 cm² (Fig. 3). Most patients were in BMI groups classified as overweight (30.88%) or obese (33.82%), as shown in figure 4.

Seven (10.29%) patients were assessed in Hospital Santa Casa de Curitiba, and the other 61 (89.71%) in Hospital de Dermatologia Sanitária do Paraná. Patients came from 16 different municipalities, with 6 (8.82%) patients from Curitiba and the remainder from municipalities of Curitiba metropolitan area. The municipality with the most share of patients in the study was Piraquara, with 29 (42.65%) patients.

History of smoking and of alcoholism were present in 33 (48.53%) and 12 (17.65%) patients, respectively, and 13 (19.12%) patients were wheelchair users. Main etiology of CLEU was venous - in 39 (57.35%) patients (Fig. 5). There was lymphoedema in 7 (10.29%) patients, five of which had primarily venous ulcers

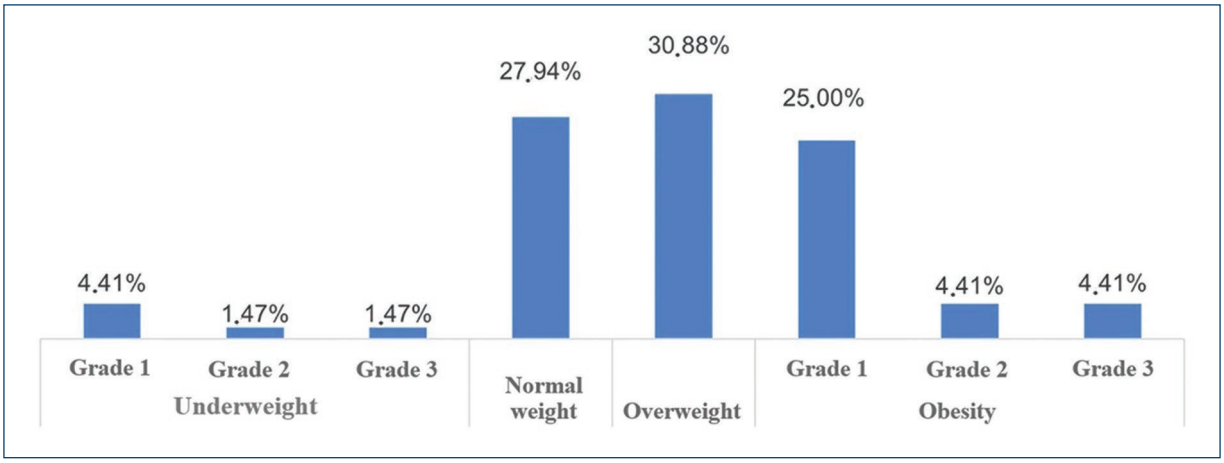

Figure 4. Distribution of CLEU patients according to WHO classification for BMI.
CLEU: chronic lower extremity ulcers; WHO: World Health Organization; BMI: body mass index.

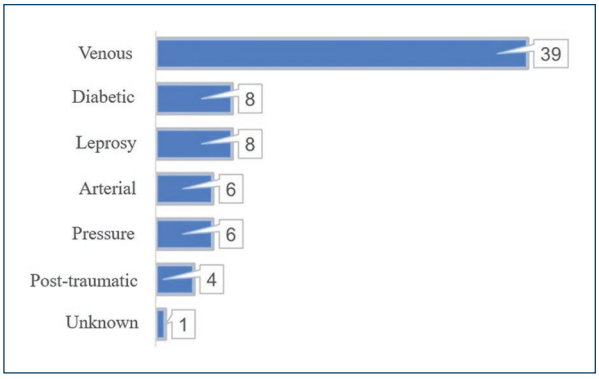

Figure 5. Distribution of CLEU patients according to wound etiology. CLEU: chronic lower extremity ulcers.

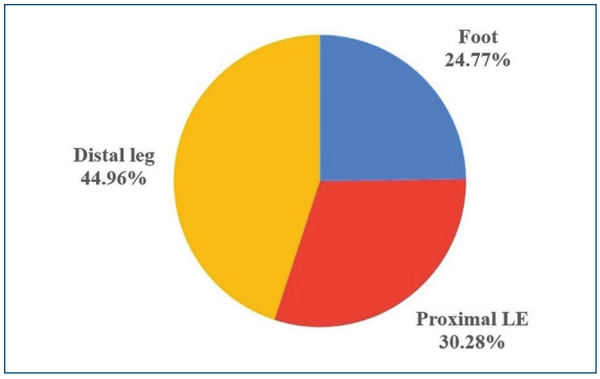

Figure 6. Site of CLEU, according to LE anatomic region.
CLEU: chronic lower extremity ulcers; LE: lower extremity.

(12.82% out of the 39 patients with venous ulcers), and two which had neuropathic leprosy ulcers (25.00% out of the eight patients with neuropathic leprosy ulcers). The most common anatomical location of CLEU was the distal leg, representing 49 (44.96%) out of the 109 assessed lesions (Fig. 6).

Duration of a CLEU was associated, with statistical significance ($p = 0.027$), to a larger wound size (Table 2). The duration had a statistically significant association also with some etiologies (Table 3): diabetic ulcers had a shorter duration ($p = 0.003$), while venous ulcers and those with lymphoedema had a longer duration ($p = 0.002$ and $p < 0.001$, respectively).

Comorbidities found in CLEU patients are described in table 4, and medications used are described in table 5.

Table 2. Correlation of quantitative variables to duration of CLEU and to size of largest wound

Duration time	Correlation coefficient*	p†
Age	–0.11	0.401
BMI	0.16	0.195
Size of largest wound	0.28	0.027
Number of wounds	0.20	0.122
Size of largest wound	**Correlation coefficient***	**p†**
Age	0.06	0.630
BMI	0.22	0.077
Number of wounds	0.20	0.109

*Spearman correlation coefficient.
†p-values obtained from Kolmogorov-Smirnov test.
CLEU: chronic lower extremity ulcers; BMI: body mass index.

Table 3. Association of duration time of CLEU to etiology and comorbidities

Duration time (years)			
Aetiology	**Mean ± SD**	**Median (minimum-maximum)**	**p***
Venous			
No	5.7 ± 9	1 (0.1-33)	0.002
Yes	13.1 ± 13.6	8 (0.1-50)	
Diabetic			
No	11 ± 12.6	6.5 (0.1-50)	0.003
Yes	0.9 ± 1	0.5 (0.2-3)	
Arterial			
No	10.4 ± 12.5	6 (0.1-50)	0.183
Yes	2 ± 1.8	2 (0.3-5)	
Pressure injuries			
No	10.2 ± 12.6	6 (0.1-50)	0.464
Yes	4.4 ± 5.5	1 (0.2-13)	
Trauma			
No	10.4 ± 12.4	6 (0.1-50)	< 0.001
Yes	0.2 ± 0.1	0.1 (0.1-0.3)	
Lymphoedema			
No	9 ± 12.5	3 (0.1-50)	0.015
Yes	15.7 ± 8.4	14 (8-31)	
Neuropathic leprosy ulcers			
No	9.4 ± 12.6	5 (0.1-50)	0.174
Yes	12 ± 10.1	9 (1-30)	
Comorbidity	**Mean ± SD**	**Median (minimum-maximum)**	**p***
Leprosy (current or previous)			
No	9.3 ± 12.7	5 (0.1-50)	0.114
Yes	12.1 ± 9.4	10 (1-30)	
DM			
No	12.5 ± 13.5	7,5 (0.1-50)	0.006
Yes	5.1 ± 8	1,5 (0.1-35)	
SAH			
No	10.8 ± 11	6,5 (0.1-33)	0.378
Yes	9.3 ± 12.8	4 (0.1-50)	
Dyslipidaemia			
No	10.1 ± 12	6 (0.1-50)	0.530
Yes	8.4 ± 13.5	5 (0.1-50)	
Other			
No	11.4 ± 12.6	8,5 (0.1-50)	0.278
Yes	8.4 ± 11.9	4 (0.1-50)	

*p-values obtained from Mann-Whitney nonparametric test.
CLEU: chronic lower extremity ulcers; DM: diabetes mellitus; SAH: systemic arterial hypertension; SD: standard deviation.

Discussion

In the present study, patients have shown a similar epidemiological profile to the one found in other publications on CLEU in Brazil. A study[5] performed in 2014 assessed 41 patients with CLEU in the city of Bauru, state of São Paulo, and the mean age of patients was 61.78 years, analogous to the one found in this study (65.10 years), with a predominance of male patients (58.54%) that was also similar to the one in this study (58.82%)[5]. In studies performed in other countries[17,19,20], there was a greater variation in the mean age of chronic ulcer patients: from 38 years in Malawi and 56.6 years in Togo, to 69.9 years in Germany – reflecting differences in life expectancy and patient profile in these populations. The majority of our patients were elderly: 72.05% were 60 years or older – a bigger rate than in other studies in Brazil, from 46.53% to 61%[4,5,24].

Table 4. Comorbidities in patients with CLEU

Comorbidity	n (%)
SAH	49 (72.06)
DM	24 (35.29)
Dyslipidaemia	15 (22.06)
Hypothyroidism	10 (14.71)
Leprosy (current or previous)	9 (13.24)
Cardiovascular disease	11 (16.18)*
Cardiac insufficiency	4 (5.88)
Atrial fibrillation	4 (5.88)
Previous AMI	3 (4.41)
Previous stroke	3 (4.41)
Rheumatic cardiopathy	1 (1.47)
Congenital heart disease	1 (1.47)
Peripheral artery disease	1 (1.47)
Neuropsychiatric disorders	7 (10.29)*
Depression	2 (2.94)
Anxiety	3 (4.41)
Schizophrenia	1 (1.47)
Epilepsy	1 (1.47)
Cognitive impairment	1 (1.47)
Musculoskeletal/osteoarticular disorders	5 (7.35)*
Fibromyalgia	1 (1.47)
Gout	1 (1.47)
Osteoarthritis	3 (4.41)
Osteoporosis	1 (1.47)
Osteopenia	1 (1.47)
Anaemia	4 (5.88)
BPH	3 (4.41)
Previous malignancy	3 (4.41)*
Leukaemia	1 (1.47)
Kaposi sarcoma	1 (1.47)
Hypopharyngeal cancer	1 (1.47)
Other	7 (10.29)*
COPD	2 (2.94)
Psoriasis	1 (1.47)
HIV infection	1 (1.47)
CKD	1 (1.47)
Gastric ulcer	1 (1.47)

*The number of patients in each group of comorbidities may not correspond to the exact sum of its lower lines, as some patients had more than one comorbidity of the same group.
CLEU: chronic lower extremity ulcers; SAH: systemic arterial hypertension; DM: diabetes mellitus; AMI: acute myocardial infarction; BPH: benign prostatic hyperplasia; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; CKD: chronic kidney disease.

In the study conducted in Bauru[5], there was a greater proportion of obese patients than in the current study: 43.90% (against 33.82%), and there was no case of low BMI (whereas 4.41% of patients in this study were underweight). Studies evaluating specifically patients with pressure injuries[21-23,27] found a higher proportion of patients with nutritional status deficiencies: 56.6% of 122 patients in the city of Aracaju, in the Brazilian state of Sergipe, were either underweight or obese[21]; and an analysis of 324 institutionalized elderly in the city of João Pessoa, in the Brazilian state of Paraíba, found that patients with a nutritional status impairment had a 3.021 odds ratio of presenting a pressure injury[22]. A multicentric study[23] assessing 473 patients in seven different Brazilian state capitals found malnutrition to be one of the main risk factors for the development of pressure injuries (odds ratio of 10.46). In that study, 98% of patients with pressure injury stage 2 or greater had some degree of malnourishment[23]. In the same way, a literature review[27] showed greater odds of pressure injuries in patients with BMI lower than 18.5 kg/m².

A minority of patients (27.94%) in our study presented BMI within the range defined by WHO as normal weight. Nevertheless, BMI is a limited method for analyzing nutritional status. It is recognized the role of validated nutritional assessment tools such as Mini Nutritional Assessment, Subjective Global Assessment, and Global Leadership Initiative on Malnutrition criteria as important in the screening of malnutrition[12,15,23,28,29]. The Mini Nutritional Assessment, for instance, seems to be the best predictor for the risk of developing pressure injuries[30]. Knowledge on a CLEU patient's nutritional status may allow interventions that will benefit wound healing, such as a hyperproteic diet and nutritional supplements with amino acids (arginine and glutamine), vitamins (A, C, D, and folic acid), and minerals[12,14].

In the present study, the rate of alcoholism was 17.65%, and the rate of smoking was 48.53%. Comparatively, smoking and/or alcoholism were present in 19.8% of 101 patients with venous ulcers in the city of Natal, in the Brazilian state of Rio Grande do Norte, and in 21.4% of 70 patients in the city of Évora, in Portugal[4]. Only 8.2% out of 122 inpatients with pressure injuries in Aracaju had a story of smoking[21]. Smoking is related to worse healing outcomes, besides contributing to the pathogenesis of some lesions, such as arterial ulcers[11,16].

With respect to the etiology of CLEU, the data shown are similar to other national publications, with venous ulcers predominance (57.35% of patients in the current study). In the city of Bauru, São Paulo, the most frequent etiology was venous (49.80% of patients), followed by neuropathic leprosy ulcers (29.30%)[5]. In the city of Juiz de Fora, in the Brazilian state of Minas Gerais, venous etiology was present in 79.0% of CLEU patients, and the second most common cause was hypertensive ulcers, present in 15.4%[24]. In Germany[17], when considering only chronic ulcers of the leg, the

Table 5. Medications used by patients with CLEU

Medication	n (%)
Antihypertensives	46 (67.65)*
ARB	22 (32.35)
ACE inhibitors	20 (29.41)
Beta blockers	13 (19.12)
Diuretics	12 (17.65)
Amlodipine	9 (13.24)
Other	2 (2.94)
Hypoglycaemic agents	24 (35.29)*
Insulin	11 (16.18)
Metformin	18 (26.47)
Other	3 (4.41)
Anticoagulants and antiplatelets	19 (27.94)
Neuropsychiatric drugs/opioids	16 (23.53)*
Opioids	7 (10.29)
Gabapentinoids	6 (8.82)
Antidepressants	5 (7.35)
Anticonvulsants	3 (4.41)
Other	3 (4.41)
Statins	15 (22.06)
Levothyroxine	10 (14.71)
NSAID and pain killers	8 (11.76)
Diosmin	8 (11.76)
Omeprazole	8 (11.76)
Vitamin and mineral supplements	7 (10.29)
Antiarrhythmics	2 (2.94)
Others	10 (14.71)

*The number of patients in each group of medications may not correspond to the exact sum of its lower lines, as some patients used more than one medication of the same group.
CLEU: chronic lower extremity ulcers; ARB: angiotensin receptor blockers; ACE: angiotensin-converting enzyme; NSAID: nonsteroidal anti-inflammatory drugs.

main etiology was venous (51.3%), followed by mixed venous and arterial (12.9%), and by arterial-only ulcers (11.0%). In the same study, vasculitis was the cause in 4.5% of lesions, pyoderma gangrenosum in 2.8%, and lymphoedema was present in 1.7% of patients[17]. The share of patients with lymphoedema here presented (10.29%) is closer to the one found in a study of 113 CLEU patients in London, published in the year 2004[31]. In such study, 77.5% of ulcers were associated to CVU, and 14.5% out of the total were associated to lymphoedema[31]. In a study with 125 inpatients with CLEU in Togo, the main etiologies were infections, responsible for 49.6% of lesions - in this population; just 16.8% of lesions were venous ulcers[19]. In the same way, infections caused 50% of chronic ulcers in 44 outpatients in Malawi[20].

Therefore, etiologies of CLEU in the studied population seem to have more similarities to that of more developed countries, except for the higher proportion of neuropathic leprosy ulcers (present in 11.76% of our patients) and of lymphoedema. Even though Brazil is the second country in the number of leprosy cases[32], there is still little knowledge concerning this disease among the general population, and late diagnosis is common, which may lead to incapacities, neuropathy, and ulcers[25]. Lymphoedema affects severely life quality and is normally associated with venous insufficiency and severe obesity. It is also frequently associated with recurrent skin and soft-tissue infections and may indicate decreased access to healthcare[17,33].

Diabetic foot ulcers and arterial ulcers are the main etiologies to be associated to an increased mortality in CLEU patients[6] and were present in 11.76% and 8.82% of evaluated patients, respectively. In the study, there were no CLEU of hypertensive etiology, due to pyoderma gangrenosum or to vasculitis.

Although etiologies of CLEU were proportionally comparable to European and North American countries, the same was not true when considering the duration of CLEU. Patients assessed in this study presented lesions for a mean time of 9.7 years – with one patient reaching a maximum of 50 years without healing. The longest-lasting wounds were mostly venous ulcers. The mean duration of CLEU was 40.8 months in Germany; and the median duration was 8 months in London, 94.2 months in the Brazilian city of Juiz de Fora, and 48 months in the Brazilian city of Bauru[5,17,24,31].

Long-lasting ulcers may express unmet needs for these patients, and greatly impair quality of life. De Oliveira Torres et al.[4] showed reduction in quality of live in CLEU patients to be considerably higher in Brazil, in a background of greater socioeconomic insecurity, than in Portugal[4]. Moreover, the CLEU itself contributes to curtail productivity and worsen socioeconomic conditions of patients, thus affecting the whole society. Estimated costs in the United States are 15 billion dollars/year for venous ulcers, and 9-13 billion dollars for diabetic foot ulcers[1].

Several factors may add to a longer duration of CLEU in the studied population. In the Brazilian public health system, there are no guidelines helping to standardize or guide care of chronic ulcers. In 2002, an international consensus[34] developed a systematic approach regarding four important factors in wound healing (TIME guidelines) – guiding debridement for remotion of devitalized tissue and wound bed preparation, infection and inflammation control, moisture imbalance, and

epithelial edge advancement[7,34]. Bacterial colonization occurs in most chronic ulcers[7], and biofilm develops in at least 60-90% of it, damaging healing due to continued inflammation even in the absence of typical local infection signs[2,7]. It is unclear to what extent biofilm treatment has been addressed in CLEU patients in Brazil.

Wound size was also bigger in the present study: the mean area was 80.0 cm², and the median area 30.0 cm². In 70.37% of cases, ulcers had areas larger than 5.0 cm². Mean ulcer size was 43.7 cm² in a study carried out in Germany in 2014, and median size was 4.0 cm² in London in 2004[17,31]. Wachholz et al. described 58.5% of patients as having lesions smaller than 4.0 cm² in Bauru, and 90% of patients described by Frade et al. in Juiz de Fora had lesions with at least one axis bigger than 5.0 cm[5,24].

Comorbidities in the present study had a similar proportion to those found in other studies, and SAH and DM were the most frequent diseases found in patients with CLEU[17,19,24,31]. Among several assessed comorbidities, Matos et al. found occurrence of pressure injuries to be possibly associated only to neurological diseases and visual impairment[22].

Limitations of this study include the fact that, as a cross-sectional study, it could not evaluate which factors could be associated to better outcomes in wound healings. Absence of a comparative control group and the small sample size may have prevented finding more statistical associations.

Conclusion

Although the clinical and epidemiological profile of CLEU patients in this study is comparable to countries in Europe and North America, there is a much larger proportion of CLEU caused by leprosy neuropathy, and of patients with lymphoedema. Duration and mean size of ulcers were larger than described in medical literature – what may indicate there is still much to improve in the care of CLEU patients in Brazil's public health system. Awareness about the influence of nutritional status on healing is important, as well as strict public health actions on smoking cessation.

Measures contributing to improved healing in these patients could benefit the entire society. CLEU is an important cause of reduced quality of life and of great morbidity and mortality, besides substantial socioeconomic costs. Even though, there are few studies about epidemiology of CLEU in developing countries such as Brazil. These studies could allow a better knowledge of the affected population, leading to better guidance on strategies for prevention and treatment. Longitudinal studies assessing factors that influence chronification of CLEU – such as nutritional status and adequate biofilm treatment – are also necessary.

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Conflicts of interest.

None.

Ethical disclosures

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

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

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.

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

Picosecond Nd:YAG laser for the removal of cosmetic tattoos of the eyebrow: a single-center retrospective review

Laser de picossegundo Nd:YAG para a remoção de tatuagens cosméticas da sobrancelha: uma revisão retrospectiva de um único centro

Manoj Pawar[1a], Assel Satvaldinova[2], and Mehak Singh[3b]*

[1]Department of Dermatology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India; [2]CHIC Clinic, Muscat, Oman; [3]VLCC Clinic, Dubai
ORCID: [a]0000-0001-6076-4908; [b]0000-0001-9180-7931

Abstract

Objective: To review the efficacy and safety of PS neodymium-doped yttrium aluminum garnet (Nd:YAG) laser for the removal of cosmetic tattoos of the eyebrows. **Method:** This was a retrospective review from January 2022 to August 2023 of patients who underwent cosmetic tattoo removal of the eyebrows with PS Nd:YAG laser. **Results:** A total of 24 patients were included in the review. 70% of patients were rated as "very much improved" (75-100% of the tattoo removed) and 30% of patients were rated "much improved" (50-75% of the tattoo removed). 1064-nm was the 1st wavelength used in all the cases. The average number of sessions required to obtain satisfactory results was 3. Four patients experienced unexpected change in their primary color of the eyebrow tattoos after the 1st treatment, which was successfully treated with 532-nm wavelength. None of the patients experienced dyspigmentation, scarring, or damage/bleaching of hairs of the eyebrows. **Conclusion:** PS Nd:YAG garnet laser is an effective and safe treatment for the removal of cosmetic tattoos of the eyebrows.

Keywords: Cosmetic. Eyebrow. Picosecond NdYAG laser. Tattoo.

Resumo

Objetivo: Revisar a eficácia e segurança do laser de picossegundo de neodímio dopado com ítrio, alumínio e granada (Nd:YAG) para a remoção de tatuagens cosméticas das sobrancelhas. **Métodos:** Esta foi uma revisão retrospectiva de janeiro de 2022 a agosto de 2023 de pacientes que se submeteram à remoção de tatuagens cosméticas das sobrancelhas com o laser de picossegundo Nd:YAG. **Resultado:** Um total de 24 pacientes foram incluídos na revisão. 70% dos pacientes foram classificados como "muito melhorados" (75-100% da tatuagem removida) e 30% foram classificados como "melhorados" (50-75% da tatuagem removida). O comprimento de onda de 1064 nm foi o primeiro utilizado em todos os casos. O número médio de sessões necessárias para obter resultados satisfatórios foi 3. Quatro pacientes tiveram uma mudança inesperada na cor principal das tatuagens das sobrancelhas após o primeiro tratamento, que foi tratada com sucesso com o comprimento de onda de 532 nm. Nenhum dos pacientes apresentou despigmentação, cicatrizes ou danos/descoloração dos pelos das sobrancelhas. **Conclusão:** O laser de picossegundo Nd:YAG é um tratamento eficaz e seguro para a remoção de tatuagens cosméticas das sobrancelhas.

Palavras-chave: Cosmético. Sobrancelha. Laser de picossegundo NdYAG. Tatuagem.

***Correspondence:**
Manoj Pawar
E-mail: manojpawar624@yahoo.com

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Introduction

Over the past few years, cosmetic tattoos, i.e., permanent makeup, have become increasingly popular throughout the world. It includes lip liner and lip color, eyeliner, hairline tattooing, areola tattooing, and eyebrow tattooing. With increased eyebrow tattooing, there is also rise in the number of patients seeking treatment to remove it safely[1]. Being a mixture of unknown pigments, which are not standardized and blended and layered by the tattoo artist, cosmetic tattoos become challenging task to treat. While dealing with such cases, it is very important to avoid side effects such as pigmentary alterations, scarring, paradoxical tattoo ink darkening, and hair bleaching or damage[1]. Before the discovery of nanosecond Q-switched lasers (QS), carbon dioxide (CO_2) and erbium-doped yttrium aluminum garnet lasers were used to ablate and thus remove the tattoo-containing dermis, but it used to cause scarring and dyspigmentation[2]. QS laser requires multiple treatment sessions and there is a higher risk of dyspigmentation, especially in darker skin type due to absorption of laser by melanin[3]. The picosecond (PS) lasers produce shorter pulse durations of 10^{-12} s resulting a greater photoacoustic effect which enable PS laser to reach the smallest tattoo particles resulting in more rapid and effective clearance. Furthermore, it affords to use lower fluences compared to nanosecond laser, thus protecting against inflammation and dyspigmentation. This specific feature also plays an important role, especially when treating cosmetically sensitive areas, such as eyebrows, where hairs may become damaged due to thermal injury[4]. Thus, PS lasers have emerged as an effective and safer treatment option for treating esthetically important areas. With this retrospective review, we aim to evaluate the efficacy and safety of PS neodymium-doped yttrium aluminum garnet (Nd:YAG) laser in the cosmetic tattoos of the eyebrows only.

Material and methods

We performed a retrospective review at a single cosmetic dermatology clinic from January 2022 to August 2023 of the patients, who underwent cosmetic tattoo removal of the eyebrows only. The patients who underwent at least 1 laser treatment session for eyebrow tattoos and returned for follow-up after the last treatment and with adequate photographic and medical record documentation were included in the study. Those with incomplete follow-up and photographic documentation and incomplete medical record were excluded from the study. Twenty-four patients met the inclusion criteria and thus were included in the study. The tattoo colors noted were black, gray, brown, and dark brown. All the tattoos were treated with a PS Nd:YAG laser (PicoWay; Candela, Wayland, MA) (Table 1). For the black, gray, and brown and dark brown tattoos, a 1064-nm wavelength was used with 3-5 mm spot size and 1.5-3.4 J/cm^2 fluence. In four cases, we used the 532-nm wavelength with 2-4 mm spot size and fluence of 0.75-1.8 J/cm^2 for orange tattoos. The efficacy and safety of PS laser was determined by two dermatologists by evaluating before-and-after photographs and medical record of each patient. Global Esthetic Improvement Scale was used to assess the clearance of tattoo were completed based on photography. Adverse events and complications were assessed through the review of medical record and photographs.

Results

In this study, 24 patients were included (all female, age range: 26-56 years, fitzpatrick skin types ranged from II-V). As the initial color of tattoos in all the patients were black, gray or brown, they were treated with the 1,064-nm Nd:YAG PS laser initially. In 4 patients (16.66%), the initial tattoo color, i.e., brownish black, changed to orange after the 1st session with 1064 nm; thus, on subsequent follow-up, it was treated with the 532-nm PS laser (range-from 1 to 4 sessions). The average number of sessions to achieve satisfactory results was 3 (range- from 2 to 6 sessions). Most of the patients (n = 8, 33.33%) achieved complete clearance of tattoos with 3 treatment sessions. Regarding patient satisfaction, 75% (n = 18) of patients were rated as "very much improved" on the Physician Global Esthetic Improvement Scale with 76-100% of the tattoo removed (Figs. 1 and 2). 25% (n = 6) of subjects were rated "much improved" with 51-75% of the tattoo clearance.

Regarding adverse events, all patients experienced immediate, transient erythema and edema of the treated area and 3 patients developed bruises near eyebrow, all of it resolved without any sequelae. Two patients (eyebrow color black) experienced hives with pruritus near eyebrows and at distant areas, few hours following the 1st treatment session and it resolved with oral antihistamines in 2 days. Interestingly, none of the patients experienced scarring, dyspigmentation, or hair bleaching or hair damage of the treated sites.

Discussion

Although QS nanosecond laser and ablative laser show efficacy in treating cosmetic eyebrow tattoos, multiple sessions are needed. Furthermore, there are undesirable side effects such as dyspigmentation, incomplete

Table 1. Parameters used for the eyebrow tattoo removal

Wavelength of picosecond Nd:YAG laser	Number of patients	Parameters used	No. of sessions = No. of patients	Note
1064 nm	24	Beam spot diameter: 3-5 mm Fluence: 1.5-3.4 J/cm^2	1 = 1 2 = 5 3 = 8 4 = 4 5 = 2 6 = 2	4 patients developed orange discoloration of tattoo 2 patients developed urticaria
532 nm	4	Beam spot diameter: 3-5 mm Fluence: 0.75-1.8 J/cm^2	1 = 1 2 = 2 3 = 1 4 = 1	

Figure 1. Black eyebrow tattoo before treatment (top) and after 3 treatments with the 1,064-nm PS laser neodymium-doped yttrium aluminum garnet laser (bottom).

Figure 2. Brownish-black eyebrow tattoo before the first treatment (left side), red-orange discoloration immediately after the 1st treatment with the 1,064-nm PS laser neodymium-doped yttrium aluminum garnet laser (right side).

clearance leading to residual tattoo, paradoxical darkening, hair bleaching, hair damage, and scarring[5]. PS lasers are more effective in clearing tattoos than QS lasers. This is due to its low pulse duration, which is less than the thermal relaxation time of the commonly used black ink in tattoos, as thermal relaxation time of carbon black in India ink is < 10 ns. PS laser pulses spare surrounding epidermis, as heat generated with pulses confined to the ink particles without significant thermal diffusion, thus making it a safer choice in darker skin types. Less number of sessions, optimum results, and good safety profile are the other benefits of PS lasers[6].

There are few studies on the treatment of cosmetic eyebrow and/or eyeliner tattoos using ablative and QS Nd:YAG lasers, whereas studies involving PS laser are scarce in literature (Table 2). Zhang et al.[12] retrospectively compared alexandrite PS laser and Nd:YAG nanosecond laser in Chinese population and found no statistically significant difference between the both lasers for removing eyeliner tattoos which were > 10 years. Moustafa et al.[15] found effective and safe clearance of brown and black ink eyebrow tattoos in four patients (3 of them were skin type IV) with the use of 532- and 1,064-nm wavelength of the PS Nd:YAG laser; however, the authors used the perfluorodecalin-infused patch during the treatment. In a retrospective review of 32 patients by Hartman et al.[16], the authors documented excellent to good response in the removal of the eyebrow cosmetic tattoos using PS 532- and 1,064-nm Nd:YAG laser after an average of only 3 treatment

Table 2. Studies involving cosmetic eyebrow tattoo removal by lasers

Study, year	No. of patients	Color of the eyebrow/ eyeliner tattoo	Laser/wavelength	No. of sessions	Results
Watts et al., 1992[7]	6	Black	QS Nd:YAG 1064 nm	2-10	Incomplete response
Fitzpatrick et al., 1994[8]	10		CO_2+30% TCA	1-2	Complete clearance
Jimenez et al., 2002[9]	1	Multicolor	QS Nd:YAG 1064 nm QS Nd:YAG 532 nm QS ruby 694 nm	1 6 5	Significant but incomplete resolution
Lee et al., 2009[10]	1	Red and brown	QS Nd:YAG 1064 nm	5	Complete clearance
Radmanesh et al., 2014[11]	20	Black and brown	Right eyebrow: CO_2, QS Nd:YAG 1064 nm QS Nd:YAG 532 nm Left eyebrow: QS Nd:YAG 1064 nm QS Nd:YAG 532 nm	1 treatment 1 treatment	75-100% improvement in 6 of 20 patients > 50% improvement in 3 of 20 patients 75-100% improvement in 1 of 20 patients > 50% improvement in 6 of 20 patients
Zhang et al., 2018[12]	72	Blue and black	755-nm alexandrite PS laser QS Nd:YAG 1064 nm	1-4 1-4	After 1 session: Excellent improvement: 25% Good improvement: 50% Excellent improvement: 12.5% Good improvement: 65.6%
McIlwee and Alster, 2018[13]	2	Blue, black, green	CO_2	1	Complete clearance
Cannarozzo et al., 2019[14]	10	Black, gray, dark pink	QS Nd:YAG 1064 nm, QS Nd:YAG 532 nm Resistant tattoos: CO_2 Fractional laser before QS Nd:YAG 1064 nm	2-10	Complete clearance
Moustafa et al., 2020[15]	4	Black and brown	QS Nd:YAG 1064 nm QS Nd:YAG 532 nm	1-4	75% clearance - 2 patients 90% clearance - 1 patient 100% clearance - 1 patient
Hartman et al., 2023[16]	32	Black and brown	PS Nd:YAG 1064 nm, PS Nd:YAG 532 nm Few cases: CO_2 Fractional laser after PS laser	1-11	On PGAIS scale Very much improved: 66% Much improved: 34%
Menozzi-Smarrito and Smarrito, 2023[17]	70	Black, red, orange, yellow	PS 755 nm and QS Nd:YAG 532 nm	1-8	Complete clearance

TCA: trichloroacetic acid; PGAIS: Physician Global Esthetic Improvement Scale.

sessions. In 2 cases, they used the CO_2 laser for faster pigment clearance, and in 1 case, 2 treatments with a CO_2 laser were performed for the removal of a yellow pigment from the persistent tattoo ink. Recently, Menozzi-Smarrito and Smarrito et al.[17], in a study of 70 patients, found complete clearance of complex eyebrow tattoos with an average of 3 laser sessions; however, for visible warm pigments (red, orange, and yellow), the number of sessions was significantly higher. In our study, we also noted complete clearance of the tattoos with an average of 3 sessions with the use of PS Nd:YAG laser. Although paradoxical darkening is observed with PS lasers, it is believed to be less common than with QS lasers. In our study, 4 patients experienced immediate orange-red discoloration after laser shots. However, with 532 PS Nd:YAG laser in 1-4 sessions, complete clearance was noted. The ability to remove specific colors has been reported to be mainly due to the specific wavelength. 532-nm wavelength is highly absorbed by orange and red color than the 1064-nm wavelength[5]. Cosmetic tattoo inks

may include mineral iron oxides (red, yellow, and black pigments) that induce color change. Titanium dioxide and ferric oxide, present in the ink particle, undergo a reduction reaction (Ti41 → Ti31 [dark violet] and Fe31 → Fe21 [black]) resulting paradoxical darkening due to high-energy, short-pulse duration of PS lasers[16]. Interestingly, our 2 patients experienced delayed hypersensitivity reactions manifesting urticarial hives that occurred near eyebrows and at a distant, untreated tattoo site, which is yet to be reported with removal of cosmetic tattoos of the eyebrow. This urticarial reaction may have resulted from an immunologic response to the ink particles, especially titanium dioxide[18].

After PS laser therapy immediate whitening i.e., cavitation bubbles occur due to the rapid heating of tattoo particles by the laser. These steam bubbles in the epidermis and dermis hinder laser-tattoo interaction; hence, multiple laser shots become ineffective. To overcome this phenomenon, perfluorodecalin-infused patches (PFDs), acoustic shock wave therapies, and R20 method (4 laser passes with a 20 min gap between each pass in a single session) have been used[15,16]. PFD patch acts as an optical clearing agent (due to similar index of refraction as that of human epidermal tissue), reducing scatter, allowing more photons to penetrate to a greater depth, and interacting with deeply residing ink particles enhancing clinical outcomes. PFD patches also provide thermal protection of the epidermis by reducing local fluence near the skin's surface[19].

The shortcomings of our study are small sample size, noncontrolled, and retrospective nature and short-term follow-up. The results might be skewed due to the retrospective nature of the study and due to variations in the parameters, especially fluence, chosen for each patient and variable number of treatments session.

Conclusion

This retrospective study has shown that the PS Nd:YAG laser was effective and safe in complete clearance of cosmetic tattoos of the eyebrows without causing scarring, dyspigmentation, and damaging hairs. Brownish black color eyebrow tattoos were prone to paradoxical darkening and changing to orange color; however, with 532-nm Nd:YAG PS laser, it was removed completely.

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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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ORIGINAL ARTICLE

Characterization of genital herpes population: a retrospective study in a tertiary center in Lisbon

Caracterização da população com herpes genital: estudo retrospetivo num centro terciário em Lisboa

Mafalda Pestana[1a], Margarida Brito-Caldeira[1], Joana Alves-Barbosa[1], Miguel Santos-Coelho[1], Ana L. João[1], Tomás Pessoa-e-Costa[1], Rita Côrte-Real[2], José M. Neves[1], and Cândida Fernandes[1]*

[1]Department of Dermatology and Venereology; [2]Department of Laboratory of Molecular Biology - Clinical Pathology. Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal
ORCID: [a]0000-0003-1361-4995

Abstract

Objective: Genital herpes (GH) is one of the most common sexual transmitted infections. Herpes simplex virus type 1 (HSV-1) genital infections have been increasing, with a shift toward its predominance in many developed countries. The aim of this study was to characterize the population with GH diagnosed in Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal. **Methods:** A retrospective analysis of all laboratory-confirmed diagnosis of GH between 2017 and 2021 was conducted. The diagnosis was established by real-time polymerase chain reaction, in samples collected by swabbing suspicious mucocutaneous lesions. Medical records of included patients were reviewed and data of interest analyzed. **Results:** During the studied period, a total of 239 patients were diagnosed with GH, from which 76.6% (n = 183) were caused by HSV type 2 (HSV-2). Most patients were men (68%; n = 163), with a mean age of 35.7 years. Compared to the group diagnosed with HSV-2, the mean age was significantly lower in the HSV-1 group (28.6 years vs. 37.9; $p < 0.001$) and the proportion of patients with first clinical manifestations of GH was significantly higher in the latest (67.8% vs. 30%; $p < 0.001$). Concomitant infection with human immunodeficiency virus was detected in 17.6% of the subjects, being significantly more prevalent among men and within the HSV-2 group ($p = 0.018$). **Conclusions:** HSV-2 remained the most common cause of GH throughout the study. Even so, similar to other European studies, HSV-1 patients were younger and the proportion of initial infection in this group was significantly higher.

Keywords: Genital herpes. Sexual transmitted infections. Epidemiology.

Resumo

Objetivo: O herpes genital (HG) é uma das infeções sexualmente transmissíveis (IST) mais comuns. As infeções genitais pelo vírus herpes simples tipo 1 (HSV-1) têm aumentado, com uma mudança no sentido da sua predominância em muitos países desenvolvidos. O objetivo deste estudo foi caracterizar a população com HG diagnosticada no Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal. **Métodos:** Foi realizada uma análise retrospetiva dos diagnósticos de HG confirmados laboratorialmente entre 2017 e 2021. O diagnóstico foi estabelecido por PCR em tempo real, em amostras colhidas por zaragatoa de lesões mucocutâneas suspeitas. Foram revistos os registos clínicos dos doentes incluídos e analisados os dados de interesse.

***Correspondence:**
Mafalda Pestaba
E-mail: mafaldambp@gmail.com

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Resultados: No período de estudo, 239 doentes foram diagnosticados com HG, dos quais 76.6% (n = 183) foram causados pelo HSV tipo 2 (HSV-2). A maioria dos doentes eram do sexo masculino (68%; n = 163), com idade média de 35.7 anos. Em comparação com o grupo diagnosticado com HSV-2, a idade média foi significativamente menor no grupo HSV-1 (28.6 anos vs. 37.9; p < 0.001) e a proporção de doentes com manifestação clínica inicial de HG foi significativamente maior neste último (67.8% vs. 30%; p < 0.001). A infeção concomitante pelo vírus da imunodeficiência humana foi detetada em 17.6% dos indivíduos, sendo significativamente mais prevalente entre homens e no grupo HSV-2 (p = 0.018). **Conclusões:** O HSV-2 foi a causa mais comum de HG durante todo o estudo. Ainda assim, à semelhança de outros estudos europeus, os doentes com HSV-1 eram mais jovens e a proporção de infeção inicial neste grupo foi significativamente maior.

Palavras-chave: Herpes genital. Infeções sexualmente transmissíveis. Epidemiologia.

Introduction

Herpes simplex virus (HSV) is one of the most ubiquitous human infections[1]. In 2016, the World Health Organization estimated that globally, 3.7 billion people under the age 50 had HSV type 1 (HSV-1) infection and 491 million people aged 15-49 had HSV type 2 (HSV-2) infection[2,3].

Genital HSV infections are a global public health problem, associated with important psychological and physical morbidity. In the last decades, genital herpes (GH) has been documented as the leading cause of genital ulcer in the sexually active population and one of the most common sexually transmitted infections (STI) worldwide[2,4]. The HSV can be transmitted via direct contact in sexual intercourse, during clinical evident episodes, or asymptomatic viral shedding. Many infections are subclinical, resulting in an underestimation of the prevalence of GH[4,5]. Primoinfection (infection in an individual without pre-existing antibodies to HSV-1 or HSV-2) and non-primary initial GH, that is, infection with one type of HSV in an individual who already has antibodies against the other type, manifest usually 4-7 days after contact, as multiple, mostly bilateral, mucocutaneous vesicles and erosions in the anogenital area[6]. These lesions are frequently associated with local pain, dysuria, and lymphadenopathy. A prodromic phase characterized by systemic symptoms such as fever, malaise, headache, and myalgia, and local burning or itching can precede the lesions[4,7]. By staying latent in the sacral sensory ganglia, the virus can reactivate and cause recurrent infections. In subsequent episodes, local and systemic symptoms are usually less severe and resolve more rapidly than in initial infections. A clinical diagnosis of GH should be laboratory-confirmed, with polymerase chain reaction (PCR) assays being the most sensitive and specific method to detect HSV-1 or HSV-2 DNA in specimens from mucocutaneous lesions. Type-specific antibodies, with a mean time to seroconversion of 3-4 weeks following an initial infection, distinguish primoinfection and non-primary initial GH from recurrent episodes and allow for diagnosis when other methods yield negative results[1]. Classically, HSV-1 has been mainly associated with orolabial infections and HSV-2 with genital ones. Although the clinical presentation of genital HSV-1 and HSV-2 infections are somewhat similar, their natural history and long-term prognosis are markedly different[8,9]. Infections resulting from HSV-1 produce fewer and milder symptomatic recurrences, and the incidence of viral shedding is much less frequent. Therefore, patients with HSV-1 GH can generally be expected to have a better prognosis and present a lower risk of transmission to sexual partners. On the other hand, HSV-2 infection is associated with more frequent recurrences, traduced in a higher risk of transmission[6,10,11]. Several studies published in recent years demonstrate a change in the epidemiology of GH, with an increasing proportion of infections caused by HSV-1[7,12-15]. This retrospective study conducted in a tertiary center in Lisbon aims to analyze and compare the epidemiological characteristics of patients with GH.

Methods

The STI clinic of the Dermatology and Venereology Department at Centro Hospitalar Universitário de Lisboa Central (CHULC) has provided venereologic services for many years. Patients may seek the clinic for screening, medical observation, and treatment of STI, without a referral and free of charge.

A retrospective and observational study was conducted to characterize the GH population in our center from January 2017 to December 2021. The results retrieved from the swabs collected for HSV infection diagnosis within this period were reviewed. The samples were collected by sterile cotton swabs of suspicious mucocutaneous lesions, that is, painful, most frequently grouped vesicles, vesicopustules, erosions

and/or ulcerations with underlying erythema. The collected samples were screened at the CHULC laboratory of molecular biology for HSV-1 and HSV-2 by real-time PCR using QuantStudio™ 5 Real-Time PCR system. From all samples yielding a positive result for HSV, only specimens collected from anogenital sites were included in our analysis. If multiple samples were collected from a given patient, only an isolate corresponding to the initial laboratory diagnosis was included in the dataset. Medical records of included patients were reviewed and their demographic data (age, gender, and nationality), sexual behavior, stage of infection (initial or recurrence), and clinical information (HIV and immune status, previous and co-STI – screening carried out if no recent screening, < 1 month) was retrieved and analyzed. The primary and non-primary initial infection was defined without use of serological tests, based on the patient's self-reported GH history and clinically presentation. Multiple scattered, bilateral, and painful lesions, tender lymphadenopathies, and systemic symptoms were considered indicators of initial GH (encompasses both primoinfection and non-primary initial infection).

Data collection and analysis were performed using Microsoft Excel 2021 and IBM SPSS version 24, respectively. Independent samples t-test was used to test differences between continuous and categorical variables at a significance level of 0.05. Non-parametric Mann-Whitney U-test was employed to evaluate differences when ordinal variables were addressed, at a significance level of 0.05. Fischer's exact test was used to test differences between two categorical variables at a significance level of 0.05, two-tailed.

Results

From January 2017 to December 2021, 11,309 patients were observed at our clinic. Of these, 239 (2.1%) had a laboratory-confirmed diagnosis of GH. HSV-2 was detected in 76.6% (n = 183) of the patients and HSV-1 in 23.4% (n = 56). The total number of GH diagnosed remained relatively stable throughout the years, with a decreasing proportion of HSV-1 infections. Analyzing the ratio of HSV-1 or HSV-2/GH infections, HSV-1 genital infections ranged from the minimum value of 16.3% (2021) to the maximum of 30% (2017), while HSV-2 infections ranged from 70% (2017) to 83.7% (2021). The clinic-epidemiological data collected are summarized in table 1, distributed accordingly to HSV type.

Demographic data

About two-thirds (68%; n = 163) of the subjects were men, with a mean age of 35.7 years (range: 17-87). The majority (60.2%; n = 144) of the patients were Portuguese. The proportion of men was higher in patients with HSV-2 (70.5%; n = 129) than with HSV-1 (60.7%; n = 34), (p = 0.169). The mean age was significantly lower in patients with HSV-1 (28.6 years; range: 17-63) than with HSV-2 (37.9 years; range: 19-87), (p < 0.001).

Sexual behavior

Regarding sexual orientation, 41% (n = 97) were men who have sex with men (MSM) or with men and women (MSMW), 31.4% (n = 75) were women who have sex with men, and 26.4% (n = 63) were MSW. In four patients, data concerning sexual orientation was not available in medical records.

Status of infection

About 39% (n = 95) of the patients sought medical observation for initial GH, this proportion being significantly higher in patients with HSV-1 (67.8%; n = 38) compared to patients with HSV-2 (30%; n = 55), (p < 0.001). Regarding clinical presentation, no global differences were noted between HSV-1 and HSV-2 genital infections.

Clinical data

Human immunodeficiency virus (HIV) infection was found in 17.6% (n = 42) of all patients, with two *de novo* diagnoses. It was significantly more prevalent among men (n = 39; 24.2%; p < 0.001), MSM/MSMW (n = 34; 35.1%; p < 0.001) and within the HSV-2 group (n = 38; 20.8%; p = 0.018). Other causes of immunosuppression such as neoplasms, end-stage kidney disease, or receiving a solid organ transplant were identified in 5% (n = 12) of the subjects.

Screening for other STI (gonorrhea, chlamydia, and syphilis) was performed in 182 of the patients. The prevalence of one or more coinfections was about 16% (n = 30), being statistically more prevalent within the group of MSM/MSMW (n = 22; 22.7%). The most common was anorectal chlamydia affecting 5.2% (n = 10), followed by anorectal gonorrhea (4.7%; n = 9).

Eighty-three patients (34.7%) had a previous diagnosis of gonorrhea, chlamydia, syphilis, and/or genital warts in

Table 1. Clinical and epidemiological characterization of GH cases, accordingly to HSV type

	HSV-1	HSV-2	Total	Statistical significance
Gender				0.169
Male	34	129	163	
Female	22	54	76	
Median age, years	28.6	37.9	36.9	< 0.001
Nationality				0.694
Portuguese	35	109	144	
Other	21	74	95	
Sexual behavior				0.591
MSW	13	50	63	
WSM	22	53	75	
MSM/MSMW	21	76	97	
NS	-	4	4	
Status of infection				< 0.001
Initial GH	38	55	95	
Recurrence	18	127	143	
NS	-	1	1	
HIV	4	38	42	0.018
Other immunosuppression	1	11	12	0.166
Concurrent STI (no. of patients affected)	7	23	30	0.719
Neisseria gonorrhoeae	2	11	13	
Chlamydia trachomatis	3	14	17	
Syphilis	2	2	4	
Previous STI (no. of patients affected)	15	68	83	0.146
Syphilis	6	39	45	
Gonorrhea	9	32	41	
Chlamydia	6	26	32	
Condyloma acuminatum	4	17	21	

GH: genital herpes; HIV: human immunodeficiency virus; HSV-1: herpes simplex virus type 1; HSV-2: herpes simplex virus type; MSM: men who have sex with men; MSMW: men who have sex with men and women; MSW: men who have sex with women; NS: not specified; STI: sexual transmitted infections; WSM: women who have sex with men.

the past. From these, the majority (82%; n = 68; p = 0.146) were diagnosed with HSV-2 GH and 77% (n = 64) were MSM/MSMW (p < 0.001). Forty-five subjects had at least one previous diagnosis of syphilis, 41 of gonorrhea, 32 of chlamydia, and 21 of *condyloma acuminatum*.

Discussion

In the last decades, the incidence of GH has increased worldwide, with an increasing proportion of HSV-1 as a causative agent in many developed countries[7,15]. In this study, HSV-2 was the main causative agent (76.6%). On the other hand, our results depicted a scenario where the proportion of HSV-1 diagnosis decreased throughout the study period, with a global prevalence of 23.4%. Interestingly, a high proportion of subjects (39.7%) in our study is from foreign countries, with a prevalence ranging from 6.7% to 8.8%. About a third of the individuals are from Asia, Africa, or America. From this last group, 87.5% had a diagnosis of GH caused by HSV-2, representing 34.4% of the HSV-2 population in the study, which aligns with a global HSV-2 seroprevalence study that observed the highest prevalence in Africa, followed by the American continent[16].

Overall and in each HSV type group, the rate of males was higher than females. Nevertheless, women represented 39% (n = 22) of the patients diagnosed with HSV-1, compared to 29.5% (n = 54) in the HSV-2 group. These data are in accordance with recently conducted studies, in which HSV-1 was most frequently isolated in young females[7,9,10,15]. For instance, in Finland, 63.6% of patients diagnosed HSV-1 GH between 2008 and 2012 were female[15].

We highlight that the mean age of patients with HSV-1 infection was significantly lower than of those with HSV-2 GH (28.6 and 37.9, respectively). Furthermore, the

proportion of patients that sought medical observation for initial GH was, proportionally, significantly higher among patients with HSV-1 (67.8%) compared to patients with HSV-2 (30%). An important fact to take into account is that genital HSV-1 infections are associated with less reactivation and clinical recurrences, with symptomatic episodes generally corresponding to initial infections[6,10,14]. An evolution toward a predominance of HSV-1 in younger people has been observed in recent studies[7,9,12,15,17]. Roberts et al. showed that HSV-1 became the most common cause of new genital HSV infections in a population of college students in Wisconsin[9]. Several factors can potentially explain the high proportion of GH in younger populations. Korr et al. pointed out the role of the decreased HSV-1 seroprevalence among children and adolescents due to improvement in hygiene and living conditions[18]. These susceptible younger populations, associated with earlier sexual debut, increased frequency of oral sex and can explain this epidemiological change in GH[1,4,7,9,12,14]. Finally, the use of condoms almost exclusively for vaginal and anal intercourse could reduce exposure to HSV-2 and consequence lower incidence in these population[9,10]. Reis et al. conducted a study to analyze trends in Portuguese adolescents' sexual behaviors, showing that the age of sexual initiation and sexual intercourse under the influence of alcohol or drugs decreased in Portugal between 2002 and 2014, while condom use increased[19].

Of note, in our study, both coinfections and history of previous STI were more frequent in patients with HSV-2 GH, with HIV infection being significantly more prevalent among this group (n = 38; 20.8%). Including HIV in the analysis, 44% of the subjects with HSV-2 had a history of previous STI, compared to 30% of the ones diagnosed with HSV-1 GH. Similar findings were observed in Spain, where Macho-Aizpurua et al. found that gonorrhea was significantly associated with GH caused by HSV-2[7,10]. Mathew et al. reported that about 79% of patients with HSV-2 infection have multiple sexual partners, a known risk factor for acquiring multiple STI[13]. Furthermore, HSV-2 infection has also been associated to a 3-fold increased risk of acquiring HIV[20]. As coinfections were statistically more prevalent within the MSM/MSMW group in our study, 41.5% of patients with HSV-2 being part of this group may constitute a confounding factor in the established association between HSV-2 and coinfections.

We recognize the limitations of our observational and retrospective study, as the data collected from a single STI center in Lisbon may not be representative at a population level. The decreasing prevalence of HSV-1 infections found over the period studied may be biased by these confounding factors. Furthermore, investigator interpretation and self-reporting bias may have occurred, since the initial episode was defined by clinical presentation and self-reported GH history registered in medical records.

Conclusion

To the best of our knowledge, no comparable studies on the clinical and epidemiological characterization of GH have been developed in Portugal. In our study, HSV-2 remained the most common cause of GH; however, HSV-1 tended to affect younger people and the proportion on initial GH was significantly higher in this group. These epidemiological particularities could have implications in clinical practice, as the natural history of HSV-1 and HSV-2, as discussed previously, is markedly different. Thus, counseling messages should emphasize the chronic character of GH and the possibility of transmission during subclinical shedding, pointing out that oral sex poses an increased risk of HSV-1 GH. Continuous attentive surveillance and systematic testing are essential to deepen our knowledge about the epidemiology of genital HSV infection.

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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 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.

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

A comparative study on the association of serum ferritin and vitamin D, and B12 levels among individuals with hair loss

Estudo comparativo sobre a associação dos níveis séricos de ferritina, vitamina D e B12 em indivíduos com queda de cabelo

Akshay J. Salecha[a], Akula V. Sai-Sameer[b], Leepika Annamreddy[c], Vobbalareddy P. Siva-Priyanka[d], Senthil Kumar-AL[e], and D.V.S.B. Rama-Murthy[f]*

Department of D.V.L, Katuri Medical College and Hospital, Guntur, Andhra Pradesh, India

ORCID: [a]0009-0009-8286-5000; [b]0009-0009-3507-5700; [c]0009-0004-8725-9062; [d]0009-0001-0746-4137; [e]0000-0003-2796-9199; [f]0009-0003-6475-5031

Abstract

Objectives: The objective of this study was to study the most frequent type of hair loss in different age groups, and the prevalent micronutrient deficiency linked to hair loss and to compare the association of serum ferritin, vitamin D, and vitamin B12 levels with hair loss among cases and controls. **Methods**: This was a cross-sectional study which included a total of 100 subjects with 50 hair loss cases and 50 age and sex-matched controls. Serum levels of vitamin D, vitamin B12, and ferritin were measured in all subjects. **Results:** Most of the subjects were between 20 and 30 years of age. There was a predominance of telogen effluvium followed by male androgenetic alopecia in all age groups. Females had considerably lower levels of serum ferritin compared to males among cases, with p-value of 0.0001. Vitamin D, vitamin B12, and serum ferritin were significantly low among cases compared to controls, with p-values of 0.0001, 0.01, and 0.006, respectively. **Conclusion**: This study suggests that low levels of serum vitamin B12 and serum ferritin and particularly vitamin D might play an appreciable role in hair loss especially telogen effluvium among females. Evaluation of these parameters could aid the clinician in opting for a more precise therapeutic modality, but identification of the exact etiology remains a primary concern as it is multifactorial, which paves path to appropriate and effective treatment.

Keywords: Hair loss. Vit D. Vit B12. Serum ferritin.

Resumo

Objectivos: Estudar o tipo de queda de cabelo mais frequente em diferentes faixas etárias e a deficiência prevalente de micronutrientes associada à queda de cabelo. Comparar a associação dos níveis séricos de ferritina, vitamina D e vitamina B12 com queda de cabelo entre casos e controles. **Métodos:** Este foi um estudo transversal que incluiu um total de 100 indivíduos com 50 casos de queda de cabelo e 50 controles pareados por idade e sexo. Os níveis séricos de vitamina D, vitamina B12 e ferritina foram medidos em todos os indivíduos. **Resultados:** A maioria dos sujeitos tinha entre 20 e 30 anos de idade. Houve predomínio do eflúvio telógeno seguido da alopecia androgenética masculina em todas as faixas etárias. As mulheres apresentaram níveis consideravelmente mais baixos de ferritina sérica em comparação aos homens entre os casos, com valor p de 0,0001. A vitamina D, a vitamina B12 e a ferritina sérica foram significativamente baixas entre os casos em comparação aos controles, com valores de p de 0,0001, 0,01 e 0,006, respectivamente. **Conclusão:** Este estudo sugere que baixos níveis séricos de vitamina B12 e ferritina sérica e particularmente vitamina D podem desempenhar um papel apreciável

***Correspondence:**
Akshay Jain-Salecha
E-mail: akshaysalecha92@gmail.com

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na perda de cabelo, especialmente no eflúvio telógeno entre as mulheres. A avaliação destes parâmetros poderia ajudar o médico a optar por uma modalidade terapêutica mais precisa, mas a identificação da etiologia exacta continua a ser uma preocupação primordial, uma vez que é multifactorial, o que abre o caminho para um tratamento adequado e eficaz.

Palavras-chave: Perda de cabelo. Vit D. Vit B12. Ferritina sérica.

Introduction

Diffuse hair loss is not an infrequent complaint encountered by dermatologists globally, which can be disquieting to patients. Hair loss or alopecia has a diversity of causes which can be due to genetics, hormone imbalances, diet, drugs, stress, infections, or other systemic conditions.

Micronutrients are crucial elements in the hair follicle cycle, playing a pivotal role in cellular turnover, with-in the matrix cells in the follicle bulb[1].

Vitamin D, a fat-soluble vitamin, is synthesized mainly by epidermal keratinocytes and dermal papillary cells through UVB-mediated conversion of 7-dehydrocholesterol to cholecalciferol in the skin, followed by further hydroxylation in the liver and kidney to 1, 25-dihydroxy vitamin D(1,25[OH]2D), the active form[2,3].

Vitamin D exerts its action through the vitamin D receptor (VDR), whose expression is required for hair follicle differentiation but not for proliferation, and its deficiency can inhibit keratinocyte differentiation and disturb the normal hair follicle cycle[4]. VDR is also required for anagen initiation[5].

Vitamin B12 has two active forms, methylcobalamin and 5 deoxyadenosyl cobalamin. It is a requisite for DNA synthesis, the formation of red blood cells, and neurological function[6].

Data suggest that vitamin B12 supports the transition of the hair follicle into anagen by increasing transcription of β-catenin through Wnt signaling and reducing transcription of glycogen synthase kinase-3, which is an inhibitor of Wnt signalling[7]. Hence, it plays a role in hair follicle proliferation.

Iron deficiency is considered the leading nutritional deficiency affecting all age groups, especially women. An abnormal balance between cellular ferritin and free iron has been suspected as a mechanism for abnormal hair growth[8], as dividing cells require higher ferritin. Serum ferritin level can be used as an early marker of iron deficiency as it is a main iron-binding protein in non-erythroid cells reflecting total body iron stores[9].

Nutrition and diet can be harnessed to treat hair loss, which represents a vital area of exploration. Studies regarding the association of deficiency of micronutrients and hair loss are still a matter of ongoing research. Providing insights into the role of micronutrients in hair loss opens better therapeutic options.

Our study aims to study the type of hair loss in different age groups and to identify the prevalent micronutrient deficiency linked to hair loss to validate their supplementation in patients with hair loss. To seek to shed light on their connection, we compared serum ferritin, vitamin D, and vitamin B12 levels in individuals with hair loss among and control cases.

Methods

This is a cross-sectional study which included 50 cases of hair loss and 50 healthy age and sex-matched controls who presented to the Dermatology Outpatient Clinic of Katuri Medical College. Cases and controls between the age group of 18-50 years who were inclined to participate were included in the study after obtaining due informed consent. Pregnancy, breastfeeding, patients with chronic medical illness, and patients not willing to participate in the study were excluded from the study. All patients were subjected to detailed clinical history, and the diagnosis was made based on a detailed physical examination by a dermatologist in the department.

Under sterile conditions with minimum atmosphere, venous blood samples were collected from an accessible vein and sent for analysis. The levels of vitamin D, vitamin B12, and serum ferritin were measured by MAGLUMI 2000 Plus Fully Automated Hormone Analyzer using the Flash Chemiluminescent Immunoassay Nanotechnology method. The normal reference intervals were 30-100 ng/mL for vitamin D, 200-1100 pg/mL for vitamin B12, and, for serum ferritin 25-350 ng/ml in males and 13-232 ng/ml in females.

Data obtained were tabulated and assessed by IBM SPSS V20 software. Continuous variables are outlined using frequency, mean, and standard deviation, while categorical variables are summarized using frequency and percentage. Means among groups were compared using an independent t-test, and proportions were compared using the Chi-square test. $P < 0.05$ was considered statistically significant.

Results

Our study included 50 cases (25 females/25 males) and 50 age and sex-matched controls between the 18 and 50 years age group. The mean age of distribution among cases was 29.68 ± 7.32, and the majority of cases (56%) affected by hair loss were found to be in the 21-30 years age group (Table 1).

Out of different causes of hair loss, telogen effluvium was diagnosed in 30 patients (60%), followed by androgenetic alopecia, 18 cases in male patients (36%), and 2 in female (4%). The distribution of diagnosis was similar.

In all age groups, females had a greater predominance of telogen effluvium, while males had a greater predominance of androgenetic alopecia.

Vitamin D, vitamin B12, and serum ferritin were significantly low among cases compared to controls, as shown in figure 1. Females had considerably low levels of serum ferritin compared to males cases (p = 0.0001), while no such difference was seen with vitamin D (p = 0.185), and vitamin B12 (p = 0.802), as depicted in table 2.

We observed low serum vitamin D levels in 62% (31 patients) of cases compared to 22% (11 patients) in controls with vitamin D level remarkably lower in cases than in controls (p = 0.0001), as shown in table 3.

Serum vitamin B12 was found to be deficient in 46% (23 patients) of cases compared to 26% (13 patients) in controls, with statistically significant lower levels in cases compared to controls (p = 0.01), as depicted in table 3.

Serum ferritin levels were low in 30% (15 patients) of cases compared to 10% (five patients) in controls, and the difference between case and control values was statistically significant (p = 0.006) (Table 3).

Out of 30 telogen effluvium cases, 20 (66%) had low vitamin D levels, 16 (53%) had low vitamin B12, and 14 (46%) had low serum ferritin levels.

Among the 18 cases of male androgenetic alopecia, 9 (50%) had low vitamin D, 7 (38%) had low vitamin B12, and 1 (5.5%) had low serum ferritin levels. On the other hand, the 2 (100%) cases of female androgenetic alopecia had low vitamin D levels, normal vitamin B12, and serum ferritin.

Table 1. Sociodemographic profile among cases and controls

Sociodemographic profile	Cases	Controls
Gender		
Male	25 (50%)	28 (56%)
Female	25 (50%)	22 (44%)
Age		
< 20	4 (8%)	3 (6%)
21-30	28 (56%)	29 (58%)
31-40	13 (26%)	16 (32%)
40-50	5 (10%)	2 (4%)
Age (mean ± SD)	29.68 ± 7.32	28.9 ± 5.02
Vitamin D	24.23 ± 12.45	34.78 ± 9.64
Vitamin B12	194.61 ± 72.75	248.38 ± 103.10
Serum ferritin	26.07 ± 13.92	32.01 ± 14.20

Table 2. Mean values of vitamin D, vitamin B12, and serum ferritin among males and females

Cases	Gender		t-value	p-value
	Male (mean ± SD)	Female (mean ± SD)		
Vitamin D	26.58 ± 13.43	21.88 ± 11.17	1.346	0.185
Vitamin B12	192 ± 72.38	197.23 ± 74.51	0.252	0.802
Serum ferritin	35.65 ± 11.31	16.50 ± 8.77	6.69	0.0001

SD: standard deviation.

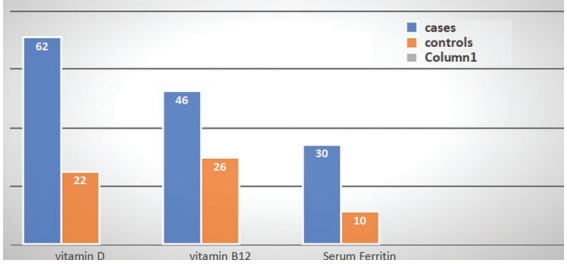

Figure 1. Comparison of percentage of vitamin D, vitamin B12, and serum ferritin deficit among cases and controls.

Discussion

Vitamin D, vitamin B12, and iron may be related to hair loss through several ascribed mechanisms. VDR activation plays a key role in the hair follicle cycle[5] and its role in hair loss needs to be emphasized. To date, iron deficiency runs the most reported nutritional cause of hair loss. Evaluation of low iron stores is done through serum ferritin levels. Vitamin B12 association with hair loss stays an ongoing debate for years.

Table 3. Vitamin D, vitamin B12, and serum ferritin percentages among cases and controls

	Vitamin D				Chi-square value	p-value
	Normal	Percentage	Deficit	Percentage		
Cases	19	38	31	62	16.42	0.0001
Controls	39	78	11	22		
	Vitamin B12				Chi-square value	p-value
	Normal	Percentage	Deficit	Percentage		
Cases	27	54	23	46	4.34	0.01
Controls	37	74	13	26		
	Serum ferritin				Chi-square value	p-value
	Normal	Percentage	Deficit	Percentage		
Cases	35	70	15	30	6.25	0.006
Controls	45	90	5	10		

After exploring all contrasting reports regarding micronutrients and hair loss, we chalked out a strategy to evaluate serum vitamin D, vitamin B12, and serum ferritin levels in all patients with hair loss.

The age of disease distribution was between 18 and 45 years, most frequently 21-30 years, with a mean age of 29.68 ± 7.32 years. The common cause of hair loss according to our study, was telogen effluvium (60%), similar to the study by Rasheed et al.[10] which included 80 female patients with a similar mean age (29.8 ± 9.3), of which 50% were telogen effluvium cases.

In this study, serum vitamin D, vitamin B12, and serum ferritin levels were significantly lower in cases with hair loss in accordance with Farah et al.[8].

There is a significant difference between cases and controls (62% vs. 22%, p = 0.0001) considering serum vitamin D, which is in accordance with a study by Rasheed et al.[10] who compared serum 25(OH)D levels in female patients with chronic telogen effluvium, female androgenetic alopecia, and healthy controls and also reported significantly lower serum 25(OH)D levels compared to the control group.

Similarly, Moneib et al.[11] reported significantly lower serum 25(OH) D levels in patients with female androgenetic alopecia than in controls, and Samar et al.[12] reported significantly lower vitamin D levels in male androgenetic alopecia cases.

Contrary to these studies, Karadag et al.[13] found significantly higher serum 25(OH)D levels in patients with telogen effluvium than in controls.

Our study showed significantly low levels of vitamin B12 among cases than controls (46% vs. 26%, p = 0.01), consistent with results reported by Ebru et al.[14], whereas Özden et al.[15] found low vitamin B12 levels in only 2% of 100 individuals with diffuse hair loss.

The present study displays a significant correlation between hair loss and serum ferritin levels when compared with controls (30% vs. 10%, p = 0.006). These low serum ferritin levels were noted specially among females when compared to males (35.65 ± 11.31 vs. 16.50 ± 8.77, p = 0.0001).

Rasheed et al.[10] also reported significantly low serum ferritin levels in both telogen effluvium and female androgenetic alopecia patients compared to controls and Tamer et al.[16] also found that hair loss is associated with low serum ferritin levels in 54 patients with hair loss compared to controls. However, on the contrary, Bregy and Trueb[17] found no association between serum ferritin level and hair loss.

Our study has certain limitations, such as a relatively small sample size (none of the pediatric age range, post-menopausal women, or elderly males are included), the absence of other types of hair loss (alopecia areata, frontal fibrosing alopecia, etc.), and the diagnosis being based only on the board-certified dermatologists' clinical experience. The study would have been more valuable if these components had been included from the study.

Conclusion

This study suggests that low levels of serum vitamin B12 and serum ferritin and particularly serum vitamin D may play

a role in hair loss, especially in telogen effluvium among females. The identification of exact etiology of hair loss remains a primary concern as it is multifactorial, which paves the path to appropriate and effective treatment, evaluation of serum levels of these nutrients could aid the clinician in opting for a more precise complementary therapeutic modality, patient-wise.

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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. 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.

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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CASE REPORT

Scurvy, a forgotten disease but still a reality: case report

Escorbuto, uma doença pouco lembrada, mas ainda uma realidade: relato de caso

Omar Algazal[1a], Gabriela Tomasi-Batiston[1b], Gabriela F. Montebello[1], João R. Antonio[1], and Eduardo C.N. Constantino[2]

[1]Department of Dermatology; [2]Department of Pathology. Hospital de Base, Faculdade de Medicina de São José do Rio Preto. São José do Rio Preto, São Paulo, Brazil

ORCID: [a]0000-0002-2683-7816; [b]0000-0001-7514-0233

Abstract

Scurvy is an uncommon disease nowadays but still presents in specific groups with hypovitaminosis. This article reports the case of an adolescent patient who started with non-specific symptoms and evolved with important systemic manifestations. The diagnosis of scurvy was not initially suspected and it was evaluated by several specialties. Several laboratory tests, imaging tests, myelograms, and biopsies were performed to exclude the differential diagnoses, until then, a serum vitamin C dosage was performed and its deficit was reported with subsequent replacement and resolution of the condition. This case demonstrates how important it is to remember this diagnosis, especially with the fundamental clues of cutaneous manifestations, such as perifollicular purpura, which are found in this disease.

Keywords: Scurvy. Vitamin C. Perifollicular purpura.

Resumo

O escorbuto é uma doença incomum atualmente, mas ainda presente em grupos específicos com hipovitaminose. Esse artigo relata o caso de uma paciente adolescente que iniciou com sintomas inespecíficos e evoluiu com importantes manifestações sistêmicas. O diagnóstico de escorbuto não foi suspeitado inicialmente e a mesma foi avaliada por diversas especialidades. Vários exames laboratoriais, exames de imagem, mielograma e biópsias foram realizadas para excluir os diagnósticos diferenciais, até que então foi realizada dosagem sérica de vitamina C e reportado seu déficit com posterior reposição e resolução do quadro. Esse caso demonstra o quão importante é lembrarmos desse diagnóstico principalmente com as pistas fundamentais das manifestações cutâneas, como as púrpuras perifoliculares, que são encontradas nesta doença.

Palavras-chave: Escorbuto. Vitamina C. Púrpura perifolicular.

***Correspondence:**
Gabriela Tomasi-Batiston
E-mail: gabriela_tomasi@hotmail.com

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Introduction

Scurvy is a pathology caused by vitamin C deficit, currently uncommon when it is compared to other nutritional disorders[1,2] and it is rarely suspected leading to delay in its diagnosis[3,4].

Scurvy is one of humanity's oldest diseases. It was first described in the Ebers papyrus, written approximately 1500 BC. Seeing whole groups of people in monasteries, within families, aboard ships, and armies afflicted with the disease, ancient writers developed multiple and varying theories regarding its etiology. Sailors were among the most affected victims, mainly in the 15th century with the beginning of long journeys[5].

British navy doctors assumed that citrus fruits such as lemons and oranges treated the disease[6], but it was not until 1931 that biochemist Albert Szent-Gyorgyi accidentally discovered a substance in lemons and oranges called "hexuronic" acid[5,6]. This was later related to the treatment of scurvy[6].

Vitamin C (L-ascorbic acid or ascorbate) is an essential nutrient for all human beings and is closely related to the maintenance of intercellular connective tissues, osteoid, dentin, and collagen. It can regulate the inflammatory response, apart from the influencing of iron absorption[4].

The clinical spectrum of scurvy is quite varied, including bone, hematological, dental, and dermatological manifestations such as petechiae and/or perifollicular purpura and follicular hyperkeratosis. The diagnosis is essentially clinical with detailed history, radiography, and laboratory tests to aid. Treatment consists of micronutrient replacement and dietary changes[1,3].

In this case, we report a patient with poor eating habits with serious clinical repercussions who was later diagnosed with scurvy.

Case report

A 13-year-old female caucasian patient with a previous history of persistent ductus arteriosus treated as a newborn was admitted to the emergency room at "Hospital da Criança e Maternidade," in São José do Rio Preto due to pain in the right hypochondrium, hypermenorrhea, and spots in the upper and lower limbs present for 3 weeks. Continued use of medications or allergies was denied. The patient is in good general condition, active, with adequate vital signs, and without alterations in the cardiopulmonary, abdominal, or neurological physical examination.

Upon dermatological examination, there were diffuse petechiae on the limbs, upper gingiva hypertrophy, and rough brownish punctiform papules disseminated on the face, limbs, and abdomen (Figs. 1-3). An incisional biopsy performed on the petechiae displayed a slight extravasation of red blood cells and hemosiderin deposits on the dermis and a mild lymphocytic inflammatory infiltrate around the vessels of the superficial plexus, compatible with non-inflammatory purpura (Figs. 4 and 5).

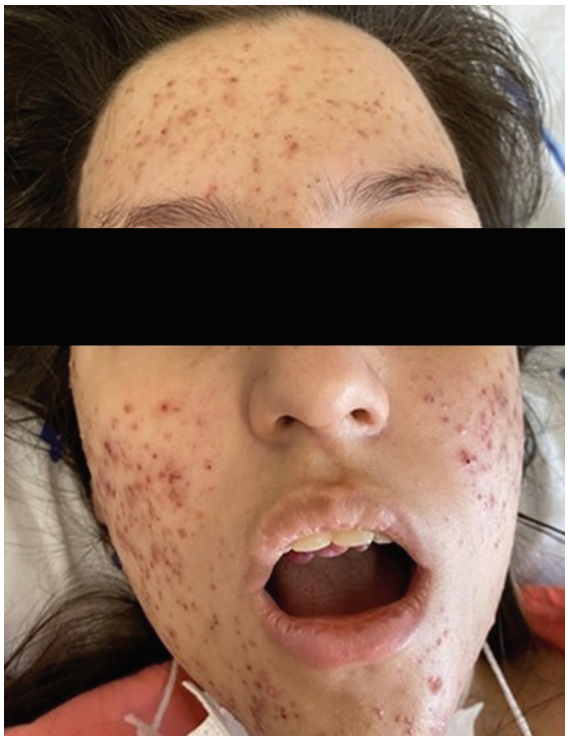

Figure 1. Patient's face showing petechiae, follicular pustules and inflammatory gingivitis.

Complementary tests highlighted only hypochromic microcytic anemia and increased fibrinogen without any changes in platelets, coagulation or inflammatory parameters, liver and kidney function, and autoantibodies. A chest X-ray and an abdominal ultrasound showed no alterations.

The patient developed pain, ankle edema, and difficulty wandering, and bone X-ray showed tenuous rarefactions in the distal metaphysis of the tibia and fibula bilaterally and more subtle changes in the femur. Ultrasound of the ankles was suggestive of an edematous/inflammatory process of the skin and subcutaneous tissue.

The hematology team performed a myelogram to exclude a lymphoproliferative disease, which showed

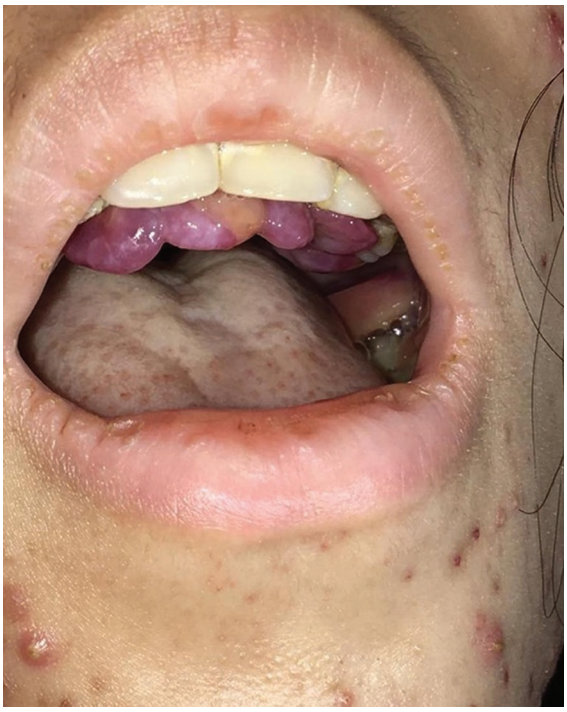

Figure 2. Oral cavity showing upper gingiva hypertrophy.

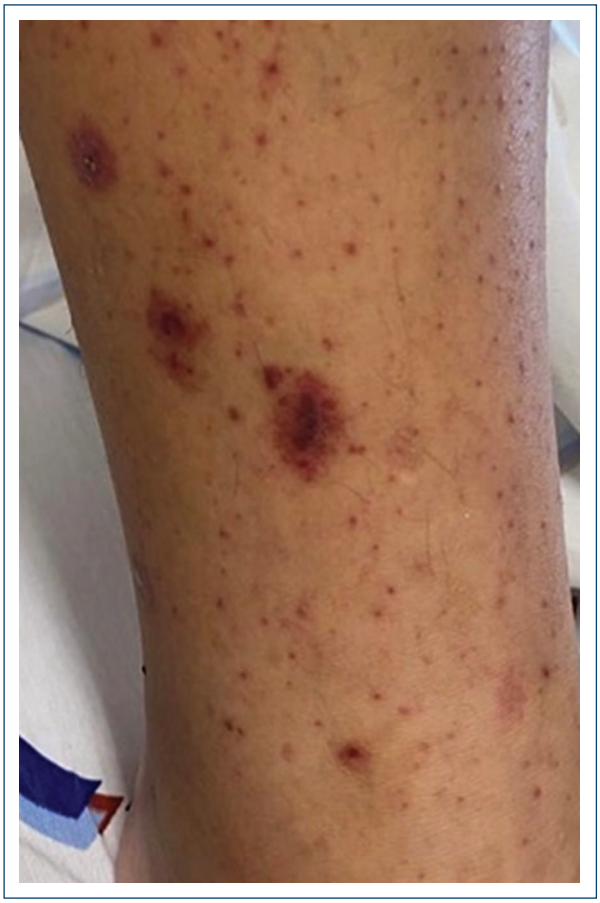

Figure 3. Multiple petechiae and perifollicular purpura on the left lower limb.

megakaryocytic hyperplasia suggestive of peripheral platelet destruction.

After a few days of hospitalization, the patient reported pain when eating and refusal of hospital food. On this occasion, the mother reported that the patient had an inadequate daily diet based on instant noodles and soft drinks. The nutritional assessment revealed an eutrophic child, but at nutritional risk with a very low serum dose of vitamin C: 0.08 mg/dL for the normal value of 0.50-1.50 mg/dL), thus diagnosing scurvy.

With vitamin C replacement, there was a gradual and complete resolution of the condition. In the first 2 weeks, cutaneous symptoms and almost all systemic symptoms cleared, whereas gingival hyperplasia showed partial improvement in the 1st month and resolution in 2 months. The patient continues to be monitored by the dermatology, nutrition, and pediatrics teams, with an improvement in dietary quality.

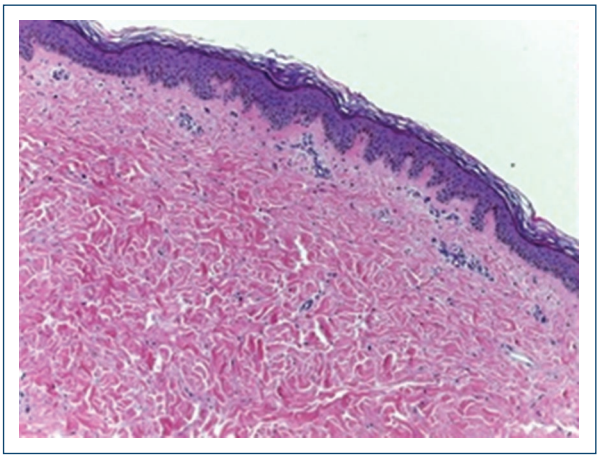

Figure 4. Perivascular and superficial lymphocytic inflammatory infiltrate (H&Ex40).

Discussion

Scurvy is a cutaneous and systemic disease caused by vitamin C deficiency, extremely rare nowadays, but it is one of the oldest diseases of humanity, with the first reports in ancient Egypt[6].

L-ascorbic acid is an essential nutrient in the diet, found in vegetables and fruits, mainly in citrus fruits,

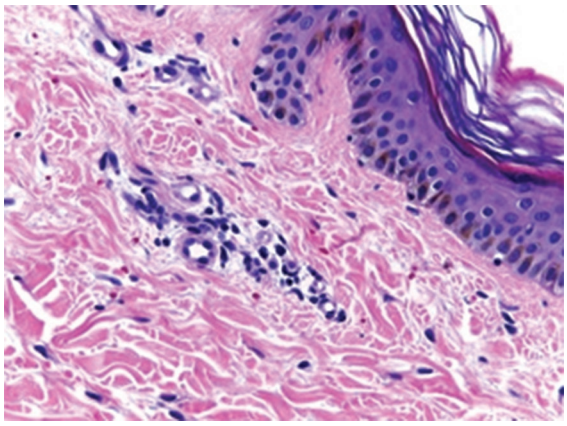

Figure 5. Extravasation of red blood cells and perivascular lymphocytic infiltrate (H&Ex100).

green vegetables, potatoes, tomatoes, and cabbage. A daily intake of 10 mg/day of vitamin C is enough to keep body stores above 300 mg[1,3]. This nutrient participates in several physiological processes and its deficit can lead to inadequate wound healing, petechiae, follicular purpura that predominate in the lower limbs, corkscrew and curved hair, subungual hemorrhages, dental defects, and osteoblast function. It may lead to pseudoparalysis in children[1,7].

Populations at risk of nutritional risk of vitamin C deficiency include the elderly, alcoholics, patients on restrictive diets, a total parenteral diet without supplementation, undergoing intestinal resections, or people who have malabsorption syndromes[8,9].

The clinical diagnosis of scurvy is confirmed by the reduction of plasma levels of vitamin C below 0.2 mg/dL. Treatment consists of oral vitamin C replacement, with doses of 300 mg/g daily, until the resolution of the clinical picture[1].

In a study by Blee et al., patients in the hospital or undergoing surgery may have borderline levels of vitamin C that can further decrease due to a lack of oral intake post-surgery or critical illnesses such as pancreatitis, sepsis, or multiple organ failure[10]. Furthermore, seven out of 12 patients who experienced widespread bleeding had poor oral nutrition before surgery.

Acute lameness, found in the pediatric population, maybe the musculoskeletal manifestation presented by scurvy due to severe malnutrition[11], as in our patient. A systematic review conducted by Trapani et al. on scurvy in the pediatric population revealed that 90% of children suffered from musculoskeletal complaints such as arthritis and lower limb pain, whereas about 33% had a limp and/or refused to walk[11,12]. Ceglie et al. also reported three cases that began with leg pain, refusal to walk, and worsened over months. Two presented gingival hyperplasia and petechiae, another reported night sweats and gingival bleeding, but after the deficit was discovered and ascorbic acid was supplemented, there was an improvement in days with further improvement within weeks[13], as in the present case.

In the current context, where consumption of ultra-processed foods with low nutritional value is increasing, scurvy is still a reality. It is a rare condition, but it must be remembered, especially if the risk factors are listed in the clinical history. Therefore, this report aims to recall the clinical and dermatological picture of scurvy. Classic findings in dermatological examination can help us with clinical reasoning, in addition to reinforcing the importance of questioning nutritional aspects in daily anamnesis.

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None.

Conflicts of interest

None.

Ethical disclosures

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

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

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CASE REPORT

Zinc supplementation possibly resolving pancreatic metastatic tumor-associated necrolytic migratory erythema. A new therapeutic approach?

Resolução de eritema necrolítico migratório associado a tumor pancreático após suplementação com zinco. Uma nova arma terapêutica?

Ana L. Matos[a], Duarte Flor, Rebeca Calado, and José C. Cardoso*

Department of Dermatology, Coimbra University Hospital Center, Coimbra, Portugal
ORCID: [a]0000-0003-1441-0601

Abstract

Necrolytic migratory erythema (NME) is a rare skin disease typically associated with glucagonoma syndrome, although it can be associated with other non-tumoral diseases. We present the case of a 71-year-old man with a pancreatic neuroendocrine tumor diagnosed with ENM. Although zinc levels were normal, after zinc oral supplementation, there was complete resolution of NME lesions that persisted even after chemotherapy with concomitant somatostatin analog therapy. This has already, although rarely, been reported. NME pathogenesis is not yet fully understood. Hyperglucagonemia contributes to the dysfunction of the epidermis but its pathogenesis most likely results from numerous aspects including hypoaminoacidemia or zinc and essential fatty acids deficiency.

Keywords: Paraneoplastic syndromes. Necrolytic migratory erythema. Zinc. Therapeutics. Pancreatic diseases.

Resumo

O eritema necrolítico migratório (ENM) é uma doença cutânea rara, tipicamente associada à síndrome do glucagonoma, embora possa associar-se a outras doenças não tumorais. Apresenta-se o caso de um homem de 71 anos com um tumor neuroendócrino pancreático que foi diagnosticado com ENM. Verificou-se resolução completa das lesões de ENM após suplementação oral com zinco, que haviam persistido mesmo após quimioterapia e terapêutica com análogo da somatostatina. Tal foi já ocasionalmente reportado. A fisiopatologia do ENM não é inteiramente compreendida. A hiperglucagonémia contribui para a disfunção da epiderme mas a sua patogénese é, provalvemente, multifatorial, incluindo determinantes como a hipoaminoacidémia ou a deficiência de zinco e ácidos gordos essenciais.

Palavras-chave: Síndromes paraneoplásicas. Eritema necrolítico migratório. Zinco. Terapêuticas. Doenças pancreáticas.

***Correspondence:**
Ana L. Matos
E-mail: ana.luisa.rodrigues.matos@gmail.com

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Introduction

Necrolytic migratory erythema (NME) is a rare skin disease typically associated with the glucagonoma syndrome, although it can be associated with other non-tumoral diseases such as nutritional deficiencies, chronic pancreatitis, or inflammatory bowel disease[1]. Glucagonomas are exceptionally rare tumors of the pancreatic alpha-cells, and their syndromic presentation includes NME, glossitis, cheilitis, venous thrombosis, diabetes mellitus, anemia, anorexia, and neuropsychiatric disorders[2]. NME treatment is closely related to oncologic treatment, with most cases showing improvement after successful tumor surgery, somatostatin analog therapy, or chemotherapy, in parallel with decreasing levels of glucagon or neuroendocrine markers[1,3,4].

Clinical case

A 71-year-old man, with no other relevant medical history, was diagnosed with a stage II pancreatic neuroendocrine tumor. A few months after surgery, a positron emission tomography-computed tomography (CT) scan showed hepatic metastasis and suggested a local relapse of the primary tumor, later confirmed by hepatic magnetic resonance and thoraco-abdominopelvic CT

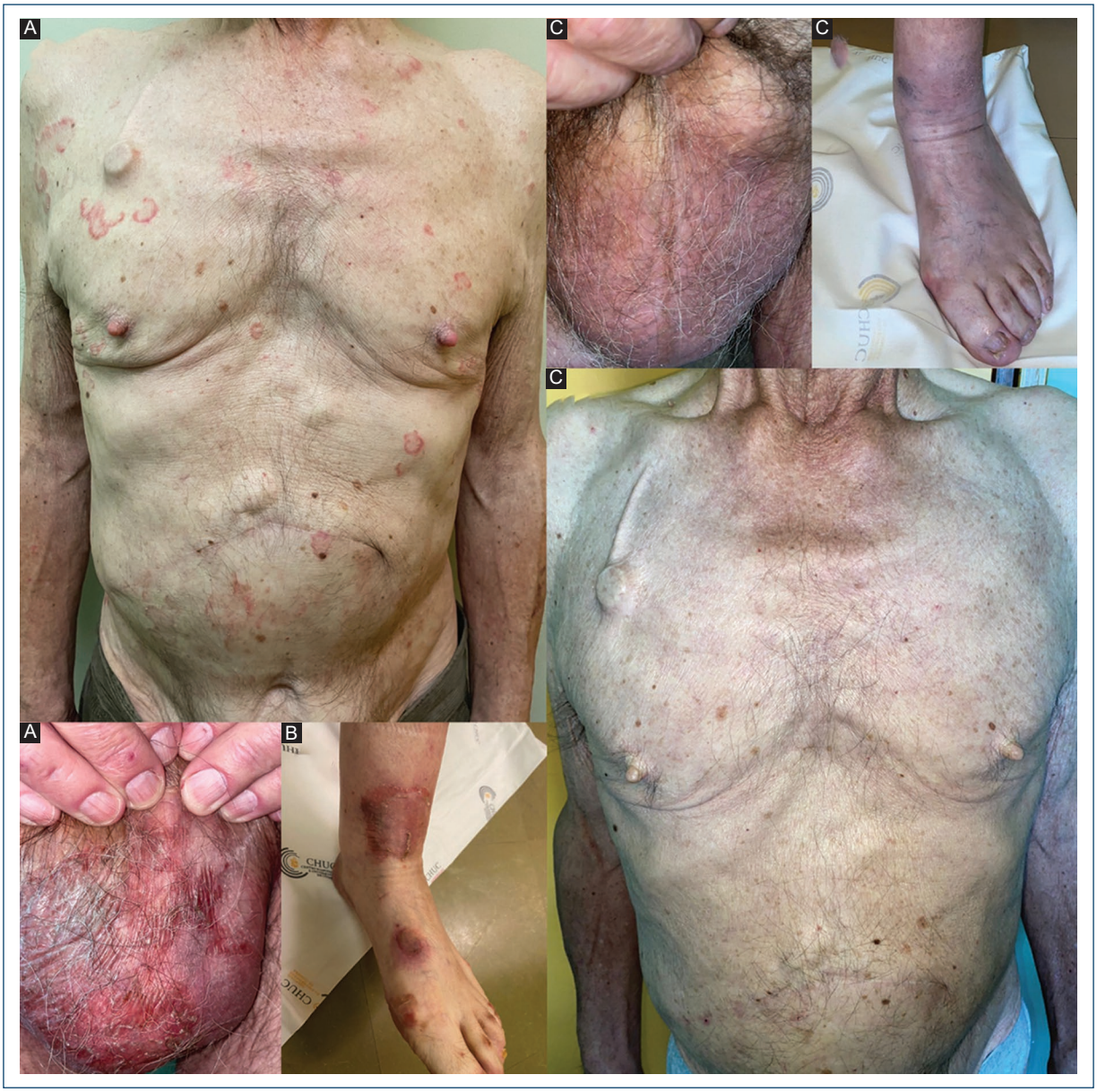

Figure 1. A: polycyclic erythematous scaly lesions, predominantly on the torso and upper limbs, also involving the genitals. **B**: large erosive, crusted, and painful plaques, also involving the feet. **C**: complete clinical resolution.

scan. The patient was then subjected to thermal ablation of liver metastases and proposed for systemic therapy with the somatostatin analog drug lanreotide. One month later, the patient was referred to the dermatology department for a 2-year worsening dermatosis. He presented with polycyclic erythematous and scaly lesions, predominantly on the torso and upper limbs, also involving the genitals, with erythematous and vaguely erosive scrotal plaques (Fig. 1A). There was no mucosal involvement, and the patient showed an adequate nutritional status. After a non-diagnostic skin biopsy, there was worsening of the dermatosis and a subsequent histological evaluation showed confluent parakeratosis, keratinocyte vacuolization with neutrophil exocytosis, and a dermal lymphomononuclear perivascular infiltrate with scattered neutrophils, confirming the diagnosis of NME. Zinc levels were normal (0.7 mg/L, normal levels between 0.66 and 1.5 mg/L) and serum neuroendocrine markers were high (neuron-specific enolase 26 ng/mL, normal levels < 15 ng/mL; chromogranin A 350.7 ng/mL, normal levels < 85 ng/mL). Glucagon levels were also significantly elevated (1295 pg/mL, normal levels < 210 pg/mL). At the time of dermatology referral, the patient also showed progression of the disease on a CT scan. For that reason, by the time, NME diagnosis was confirmed, he began chemotherapy with capecitabine and temozolomide, maintaining lanreotide therapy. A month later, he maintained significant skin lesions, mainly affecting the lower limbs, with large erosive, crusted, and painful plaques, also involving the feet (Fig. 1B). Hepatitis C serology was negative. Zinc supplementation was initiated at a 220 mg twice daily dose for 2 months. At 3-month follow-up, there was a complete resolution of the dermatosis (Fig. 1C).

Discussion

NME pathogenesis is not yet fully understood. Hyperglucagonemia contributes to the dysfunction of the epidermis but most likely numerous aspects including hypoaminoacidemia or zinc and essential fatty acids deficiency are involved in the pathogenesis of NME. In our patient, after zinc oral supplementation, in the context of normal serum zinc levels, there was complete resolution of NME lesions that had persisted even after chemotherapy with concomitant somatostatin analog therapy. This has already been reported[5], although rarely, and supports the role of zinc deficiency in the pathogenesis of NME.

Conclusion

In our patient, after zinc oral supplementation, in the context of normal serum zinc levels, there was complete resolution of NME lesions that had persisted even after chemotherapy with concomitant somatostatin analog therapy. This has already been reported, although rarely, and supports the role of zinc deficiency in the pathogenesis of NME.

Funding

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Conflicts of interest

None.

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CASE REPORT

Panniculitis in reactivation of Chagas disease in a cardiac transplant patient

Paniculite na reativação da doença de Chagas em paciente transplantado cardíaco

Gabriela T. Batiston[1a], Gabriella B. Pintos[2], João R. Antonio[1], Eduardo C.N. Constantino[3], and Daniel Villafanha[4]*

[1]Department of Dermatology; [2]Faculdade de Medicina; [3]Department of Patology; [4]Department of Cardiology. Hospital de Base, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, São Paulo, Brazil
ORCID: [a]0000-0001-7514-0233

Abstract

Reactivation of chronic Chagas disease is a rare condition, occurring solely in immunosuppressed patients. Skin involvement has been reported in patients with chronic Chagas disease and heart or kidney transplantation who reactivated the trypanosomiasis. In all cases involving the skin, amastigote forms of *Trypanosoma cruzi* are detected. Our case focuses on a 51-year-old female with a history of cardiac transplantation due to Chagas disease and immunodepression. The dermatology team was consulted due to the presence of painful erythematous nodules, after 30 days of hospitalization. Initially, a skin biopsy suggested cutaneous leishmaniasis as a hypothesis. However, subsequent immunohistochemistry confirmed the presence of *T. cruzi*, leading to the decision to treat for Chagas disease reactivation. The development of panniculitis is not commonly associated with Chagas disease. This case underscores the importance of not disregarding such possibilities and highlights the necessity for histopathological and immunohistochemical analyses to complement the diagnostic process.

Keywords: Panniculitis. Chagas disease. *Trypanosoma cruzi*. Cardiac transplant.

Resumo

A reativação da doença de Chagas crônica é condição rara e ocorre apenas em pacientes imunossuprimidos. O envolvimento da pele foi reportado em pacientes com doença de Chagas crônica e transplante hepático e cardíaco com reativação da tripanossomíase. Em todos os casos cutâneos foi detectada a forma amastigota do *Trypanosoma cruzi*. Nosso caso traz paciente feminina de 51 anos com história de transplante cardíaco devido à doença de Chagas e imunodepressão. A equipe dermatológica foi chamada devido ao aparecimento de nódulos eritematosos dolorosos, após 30 dias de hospitalização. Primeiramente, a biópsia de pele foi compatível com hipótese de leishmaniose cutânea. Depois da imuno-histoquímica, confirmou-se a presença de *T. cruzi*, sendo decidido tratar reativação da doença de Chagas. O desenvolvimento de paniculite não é usualmente associado à doença de Chagas. Assim, ressalta-se a importância de não excluir tal diagnóstico e refere a necessidade da análise anatomopatológica e imuno-histoquímica para complementação diagnóstica.

Palavras chave: Paniculite. Doença de Chagas. *Trypanosoma cruzi*. Transplante cardíaco.

Correspondence:
Gabriela T. Batiston
E-mail: gabriela_tomasi@hotmail.com

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Introduction

Chagas disease is an endemic trypanosomiasis in South and Central America. Reactivation of chronic Chagas disease is a rare condition that exclusively occurs in immunosuppressed patients[1]. Skin involvement has been reported in patients with chronic Chagas disease following heart or kidney transplantation, leading to the reactivation of trypanosomiasis. Skin lesions typically manifest as rashes on the lower limbs and painful nodules that eventually progress to ulceration. Amastigote forms of *Trypanosoma cruzi* are consistently detected in the skin in all cases of cutaneous involvement commitment[2].

Infective panniculitis refers to inflammations of the subcutaneous fat induced by various microorganisms. The immunosuppressed population is on the rise due to factors such as HIV infection, organ transplantation, and the widespread use of immunosuppressive drugs. This increase has led to a higher incidence of common skin infections, making opportunistic pathogen infections more prevalent and resulting in atypical presentations, including panniculitis[3].

These cutaneous manifestations typically present in a non-specific manner within the immunosuppressed population. Presentation characteristics are strongly influenced by the virulence of the specific organism and the immune status of the host. Therefore, diagnosing panniculitis requires both microbiological and histological studies[3].

Case report

A 51-year-old female patient with a history of cardiac transplantation due to Chagas disease and immunosuppression was admitted to the hospital due to acute myocardial cellular rejection. Her medical history included hypertension, chronic kidney disease, intermittent atrial fibrillation, and type 2 diabetes mellitus. She was being treated with mycophenolate sodium (720 mg every 12 h), cyclosporine (50 mg every 12 h), acetylsalicylic acid (100 mg once a day), atorvastatin (40 mg once a day), amiodarone (200 mg once a day), nifedipine (10 mg every 12 h), metformin (850 mg once a day), and rivaroxaban (100 mg once a day).

The patient underwent an elective endomyocardial biopsy due to complaints of worsening dyspnea, palpitations, and dry cough. She was hospitalized following the diagnosis of Grade 2R moderate acute cellular rejection (immunohistochemistry CDd negative, CD3 positive, CD20 positive, and CD68 positive).

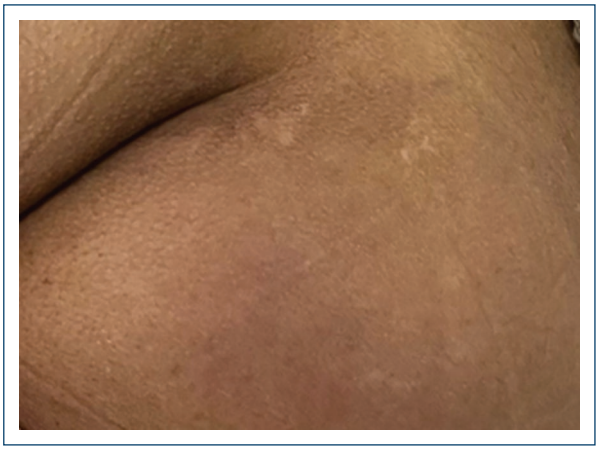

Figure 1. Erythematous nodules on glutes, more tangible than visible.

However, during her hospital stay, she developed a daily fever. Infectious screening was conducted, and treatment with ganciclovir for cytomegalovirus was initiated due to positive test results, in addition to antibiotic therapy with ceftriaxone. Her condition continued to deteriorate, leading to pancytopenia and worsening of fever spikes.

After 30 days of hospitalization, the patient noticed painful erythematous nodules measuring between 2 and 4 cm on her legs, glutes, and lower abdomen (Fig. 1). The dermatology team was consulted, and they suspected panniculitis. A deep biopsy of the lesion in the posterior region of the left lower limb, involving the subcutaneous tissue, was performed using a 4-mm punch, and histopathological analysis was requested.

The dermatology team considered several diagnostic possibilities, including panniculitis of inflammatory or infectious origin, erythema nodosum secondary to medications or infections, erythema induratum, and vasculitis.

Initially, amastigote forms were observed in the histopathological analysis, suggesting the hypothesis of cutaneous leishmaniasis. However, after immunohistochemistry, the presence of *T. cruzi* was confirmed in skin and subcutaneous samples (Fig. 2), and polymerase chain reaction was positive for Chagas disease.

During hospitalization due to Chagas disease reactivation, the patient was initially treated with corticosteroid pulse therapy (methylprednisolone, followed by prednisone), and following the diagnosis, she received benznidazole (100 mg every 12 h) for 60 days. In addition, she received immunosuppressive therapy due to

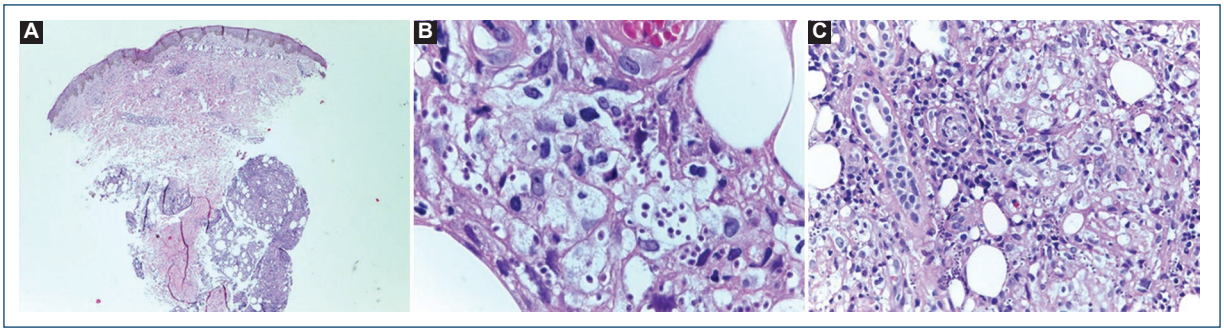

Figure 2. A-C: left gluteal biopsy. **A:** epidermis with foci of basal layer degeneration. The superficial and deep dermis exhibits perivascular lymphocytic inflammatory infiltrate. The hypodermis exudes an inflammatory infiltrate with a predominance of macrophages, presence of amastigote form of *Trypanosoma cruzi* and lobular panniculitis (H&E stain, magnification ×4). **B and C:** presence of amastigote form of *T. cruzi* and lobular panniculitis (H&E stain, magnification ×100).

her heart transplant, involving cyclosporine and sirolimus, as well as prophylaxis with antibiotics (bactrim, vancomycin, and teicoplanin) and antiviral medication (ganciclovir).

At present, the patient is under follow-up at the reference center, with no Chagas disease relapses following the established treatment and no further complications since the last hospitalization.

Given the rarity of the case, the cardiology, dermatology, and infectious disease teams were consulted for discussion, and it was decided to initiate treatment for the reactivation of Chagas disease. The patient showed improvement in the panniculitis after starting treatment.

Discussion

The case presented involves a patient who experienced an unusual manifestation of *T. cruzi* reactivation following immunosuppressive therapy. Reactivation of Chagas disease entails a transition from a latent or chronic state, in which the patient is stable, to an acute condition marked by increased parasitemia and serologic titers, leading to more severe lesions[4]. Typically, manifestations have been described as myocarditis, panniculitis, meningoencephalitis, and brain abscess, with myocarditis being the most frequent presentation[5].

In immunosuppressed patients, the reactivation of Chagas disease can take on an atypical form, characterized by dermatologic symptoms and various skin lesions. These can include indurated erythematous plaques with necrosis in different areas, erythematous papules and nodules, skin ulcers, or panniculitidis[4], as observed in the reported case.

In such cases, the amastigote forms of *T. cruzi* are not easily identified using common stains such as hematoxylin and eosin[6]. In some endemic areas, such as Brazil[6,7], they must be differentiated from agents causing leishmaniasis, particularly in cases involving cutaneous lesions. Immunohistochemistry is a valuable tool for making this distinction, as was the case in our reported case, where this analysis enabled the correct diagnosis, especially after unsuccessful attempts to detect the parasite in peripheral blood and endomyocardial biopsy. Polymerase chain reaction was also crucial in confirming the recurrence of Chagas disease[5].

The administration of antiparasitic treatment for symptomatic or oligosymptomatic patients with chronic Chagas disease is justified to attempt to eradicate the parasite. This is particularly important in infected patients who may later become organ donors or recipients of transplants and in those who, due to various causes of immunocompromised, may experience dissemination and/or acute infectious conditions[4].

Despite its atypical presentation, the reported case underscores the importance of not disregarding such possibilities and emphasizes the need for histopathological and immunohistochemical analyses to complement the diagnostic process.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of people and animals. The authors declare that for this investigation, no experiments were carried out on human beings and/or animals.

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CASE REPORT

A case of autoimmune progesterone dermatitis

Um caso de dermatite autoimune à progesterona

Ana G. Lopes[a], Catarina Cerqueira, Carlos Nogueira, Joana Gomes, and Celeste Brito*

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

Abstract

A 41-year-old female patient presents to the dermatology department with a 3-year history of a monthly relapsing pruritic eruption. These lesions appear 5-7 days before the onset of menses and resolve 3-4 days after menstruation. During her two previous pregnancies, she had no symptoms. She had been previously treated with antihistamines and oral corticosteroids with only temporary relief. On examination, during the luteal phase, the patient presented multiple maculopapular pruritic wheals distributed throughout the body. Several laboratory studies were performed and were all normal or negative, including auto-antibodies tests and hormonal analysis. Patch tests with the standard series of the Portuguese Contact Dermatitis Group, corticosteroid series, and metal series revealed positive reactions to nickel sulfate (++) and palladium chloride (+) at 72 h. An intradermal test with medroxyprogesterone at concentrations of 0.1 and 10 mg/mL was performed on the 7th day of the menstrual cycle. The test was positive 2 h after the injection and persisted for 24 h. The diagnosis of autoimmune progesterone dermatitis was made and the patient started tamoxifen 40 mg/day, with almost complete clinical clearing. Four months after, the dose was reduced, with no relapsing. Six months later, the patient remains free of symptoms.

Keywords: Autoimmune progesterone dermatitis. Progesterone. Autoimmune urticaria. Urticaria. Intradermal test.

Resumo

Descreve-se o caso de uma doente do sexo feminino de 41 anos, previamente saudável, sem antecedentes de dermatite atópica ou dermatite alérgica. A doente é avaliada na consulta de dermatologia por uma erupção pruriginosa recorrente, mensal, com 3 anos de evolução. Essas lesões geralmente apareciam 5 a 7 dias antes do início da menstruação e desapareciam aproximadamente 3 a 4 dias após o período menstrual. A doente referiu que quando esteve 2 vezes grávida e não teve sintomas nesse período. Ela tinha sido previamente tratada com anti-histamínicos e corticosteroides orais, com apenas alívio temporário. Ao exame físico, durante a fase lútea do período menstrual, a doente apresentava múltiplas maculopápulas eritematoedematosas, pruriginosas, distribuídas por todo o corpo. Vários estudos laboratoriais foram realizados e todos estavam normais ou negativos, incluindo testes de autoanticorpos e análises hormonais. Testes epicutâneos com a série padrão do Grupo Português de Dermatite de Contato (GPEDC), série de corticosteróides e série de metais revelaram reações positivas ao sulfato de níquel (++) e cloreto de paládio (+) às 72 horas. Foi realizado um teste intradérmico com medroxiprogesterona nas concentrações de 0.1 e 10 mg/mL no 7º dia do ciclo menstrual. O teste foi positivo 2 horas após a injeção e persistiu por 24 horas. Foi feito o diagnóstico de dermatite autoimune à progesterona e a doente foi tratada com tamoxifeno 40 mg/dia, com praticamente completa resolução clínica. Quatro meses após, a dose foi reduzida, sem recaída. Seis meses depois a doente continua sem sintomas ou efeitos adversos.

Palavras-chave: Dermatite autoimune à progesterona. Progesterona. Urticária autoimune. Urticária. Teste intradérmico.

***Correspondence:**
Ana G. Lopes
E-mail: ana.gabriela.castro@hb.min-saude.pt

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Introduction

Autoimmune progesterone dermatitis (APD) is a rare, cyclical, and mucocutaneous hypersensitivity reaction to peak levels of endogenous progesterone seen in women, in the luteal phase of the menstrual cycle. It is an underdiagnosed, complex disease associated with high morbidity[1]. Therefore, recognition of this process is important as it can result in significant quality of life impairment among women.

Our case report describes one of the rare cases of APD, manifesting as urticarial lesions.

Clinical case

We describe the case of a 41-year-old female patient, previously healthy, with no history of atopic or allergic dermatitis. She was not taking any medication and there was no history of atopic or allergic contact dermatitis.

The patient presented to the dermatology department with a 3-year history of a monthly relapsing pruritic eruption. The patient stated these lesions usually appeared 5-7 days before the onset of menses and resolved approximately 3-4 days after menstruation. She had been previously treated with antihistamines and oral corticosteroids with only temporary relief.

She had had no symptoms during her two pregnancies and she used an intrauterine copper device as a birth control method. There was no history of dysmenorrhea, menstrual irregularities, or oral contraceptive use.

On examination, during the luteal phase, the patient presented multiple maculopapular pruritic non-evanescent wheals distributed symmetrically throughout the body, lasting for more than 24 h, compatible with urticarial lesions.

Several laboratory studies were performed and were all normal or negative, including: ANA, anti-DNA, Sm, SSa, SSb, and RNP antibodies; C3, C4, CH100, and C1-inhibitor; thyroid stimulating hormone, T3, and T4; immunoglobulin G, immunoglobulin A, immunoglobulin M, and immunoglobulin E (IgE).

Hormonal analysis collected at day 3 and day 21 of the menstrual cycle revealed progesterone and estradiol serum levels were also normal during the follicular (1.57 ng/mL and 49.8 pg/mL, respectively) and the luteal phase (2.65 ng/mL and 64.3 pg/mL, respectively).

With the suspicion of APD an intradermal test with 0.1 mL of an 150 mg/mL aqueous solution of medroxyprogesterone serially diluted with 0.9% sodium chloride to concentrations of 0.1 and 10 mg/mL was performed on the 7th day of the cycle. A positive reaction was observed within 2 h, remaining positive for about 24 h (Figs. 1 and 2).

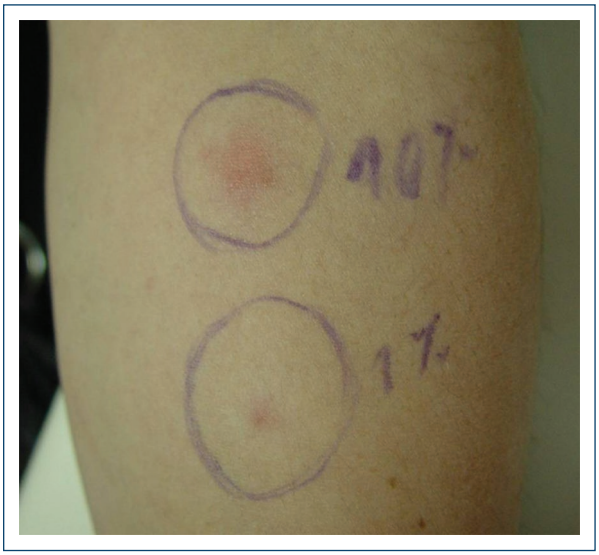

Figure 1. Intradermal test with aqueous solution of medroxyprogesterone (concentrations of 0.1 and 10 mg/mL) 2 h after.

Patch tests were also performed, with the same medroxyprogesterone solution, the standard series of the Portuguese Contact Dermatitis Group, corticosteroids series, and metal series, which revealed positive reactions only to nickel sulfate 5% pet (++) and palladium chloride 1% pet (+) (Fig. 3).

The diagnosis of APD was made and the patient was treated with tamoxifen 40 mg/day, with almost complete clinical clearing. Four months after the dose was reduced to 20 mg/day, with no relapsing and subsequently to 10 mg/day. Six months later, the patient remains free of symptoms and with no side effects.

Discussion

APD is an extremely rare disease, characterized by recurring dermatologic manifestations during the luteal phase of the menstrual cycle[2]. APD has also been reported to be triggered by exogenous progesterone exposure or pregnancy, with peripartum onset and flares in a subset of patients[3]. In this case, the patient had no symptoms while she was pregnant.

The cause of APD is not known. It seems exogenous progesterone exposure, such as those used for oral contraception pills or *in vitro* fertilization, is an important cause of morbidity and may stimulate the body to form progesterone-specific IgE antibodies,

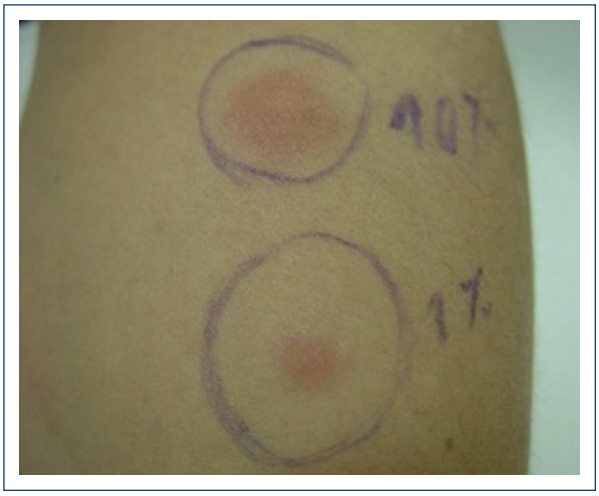

Figure 2. Intradermal test with aqueous solution of medroxyprogesterone (concentrations of 0.1 and 10 mg/mL) 5 h after.

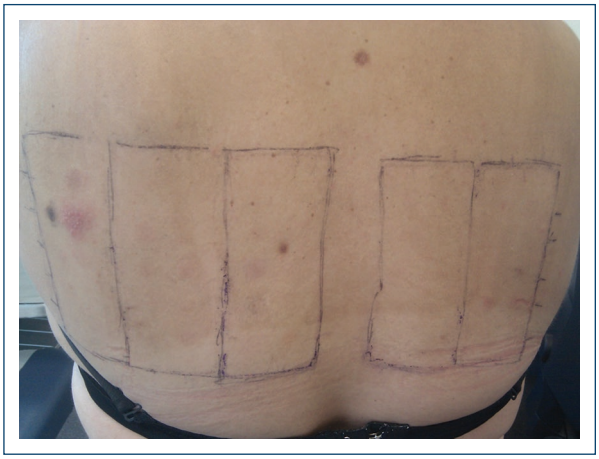

Figure 3. Patch testing.

that cross-link activate mast cells resulting in APD[4]. However, not all patients with this disease have a history of exposure to exogenous progesterone, as in the case we just described.

APD can have many different presentations including recurrent and cyclical urticaria with or without angioedema, anaphylaxis, pruritus, and dermatitis. Other presentations include vesiculobullous disorders, erythema multiforme, fixed drug eruptions, aphthous stomatitis, maculopapular rash, and recalcitrant dermatitis[5-7]. The lesions are characteristically symmetrical and occur on the face, trunk, and extremities. Our patient presented with urticarial lesions, which is one of the most common manifestations of this dermatitis.

The mean age at the beginning of symptoms is 27.3 years[6]. Symptoms usually appear 3-4 days before menstruation when progesterone levels peak and resolve within a few days after the onset of menstruation as progesterone levels reduce, only to recur just before the next period[1], as in this case.

Diagnosis is difficult and often delayed. It is frequently made based on the exclusion of all possible differential diagnoses.

The diagnostic criteria for APD proposed by Warin are: skin lesions related to menstrual cycle; symptomatic improvement after inhibiting progesterone secretion by suppressing ovulation; positive response to intradermal testing with progesterone[8]. Intradermal progesterone tests may be used to help diagnose APD; however, the test is not standardized, has unknown sensitivity and specificity, and test results do not typically change management. In a series of 24 cases of APD, only 50% of patients showed a positive result to this test. In patients presenting with urticaria and/or anaphylaxis, the intradermal skin test may potentially be of more value[9]. In this case, we performed an intradermal test with an aqueous solution of medroxyprogesterone at concentrations of 0.1 and 10 mg/mL on the 7th day of the menstrual cycle, and it was positive.

In regards to treatment, primary treatment includes prescribing a combination of oral contraceptives. Other successful treatment options include gonadotropin-releasing hormone agonists, danazol and tamoxifen; topical and oral antihistamines and steroids to treat cutaneous symptoms; and bilateral oophorectomy in patients experiencing persistent symptoms[2]. Here, the patient was treated with tamoxifen with complete resolution of symptoms.

Conclusion

The diagnosis of APD still remains a challenge, contributing to a significant delay in diagnosis, requiring further clarification of criteria and development of accurate diagnostic tests. Recognition of this rare condition needs a high index of suspicion.

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.

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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CASE REPORT

Primary cutaneous anaplastic large-cell lymphoma: case report

Linfoma anaplásico de grandes células cutâneo primário: relato de caso

*Louise Knauber[1a], Rubia N. Alves-Ramos[1b], Melyssa Grignet-Ribeiro[2c], Dirceu E. Teixeira-Pinto[3d], and Eduardo Morais-de Castro[1e]**

[1]Department of Medicine, Faculdades Pequeno Príncipe; [2]Department of Pathology, Hospital Erasto Gaertner; [3]Department of Surgical Oncology, Hospital Ônix. Curitiba, Brazil

ORCID: [a]0009-0004-7375-7546; [b]0000-0003-0068-7597; [c]0000-0001-7922-141X; [d]0009-0001-2745-1966; [e]0000-0001-6136-2660

Abstract

Primary cutaneous anaplastic large-cell lymphoma (C-ALCL) is a rare subtype of non-Hodgkin lymphoma, CD30 positive that does not exhibit extracutaneous manifestations at the time of diagnosis. The emergence of solitary papules or nodules, on the trunk and extremities, characterizes the disease. This case reports a 58-year-old female who presented with a rapidly enlarging nodule on her right calf. The biopsy revealed a malignant neoplasm of large cells. The morphological features, combined with the immunohistochemical profile, revealed a CD30-positive and anaplastic lymphoma kinase-negative lymphoproliferative disorder, consistent with C-ALCL. Shortly after the first excision, new lesions manifested in violaceous papules and nodules, and a new biopsy was performed, confirming the initial diagnosis. The patient underwent radiotherapy for 4 weeks and the lesions regressed but recurred about a year after. The patient is currently under treatment. The main goal is to emphasize the importance of considering this diagnosis as a possibility in large-cell cutaneous lymphomas.

Keywords: Case report. Anaplastic large-cell lymphoma. Cutaneous lymphoma. Dermatology. Hematology.

Resumo

O linfoma anaplásico de grandes células cutâneo primário (C-ALCL) é um linfoma não-Hodgkin raro com expressão do antígeno CD30 e que não possui manifestações extracutâneas no momento do diagnóstico. O surgimento de pápulas ou nódulos solitários, localizados principalmente no tronco e nas extremidades, são característicos da doença. Neste relato de caso, discorre-se sobre paciente do sexo feminino, 58 anos, com lesão em panturrilha direita de aspecto nodular com crescimento acelerado. Na biópsia, anatomopatológico evidenciou neoplasia maligna de células linfoides/epitelioides. Os aspectos morfológicos, associados ao perfil imunoistoquímico, revelaram desordem linfoproliferativa CD30 positiva em pele, compatível com C-ALCL. Após primeira exérese, surgimento de novas lesões dolorosas em placa de coloração violácea, com realização de nova biópsia. Foi realizada radioterapia durante quatro semanas e as lesões regrediram, porém, recidivaram cerca de um ano após o tratamento. Houve indicação de um novo ciclo de radioterapia para a paciente. A excepcionalidade do C-ALCL justifica o desenvolvimento desse relato de caso, a fim de salientar a importância de se considerar este diagnóstico como uma possibilidade nos linfomas cutâneos de grandes células.

Palavras chave: Relato de caso. Linfoma anaplásico de células grandes. Linfoma cutâneo. Dermatopatologia. Hematopatologia.

***Correspondence:**
Eduardo Morais-de Castro
E-mail: medmoca@gmail.com

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Introduction

Primary cutaneous anaplastic large-cell lymphoma (C-ALCL) is a rare subtype of non-Hodgkin T-cell lymphoma with exclusively cutaneous onset and location[1], composed of large, atypical lymphocytes of either pleomorphic, anaplastic or immunoblastic cytomorphology, and expression of the CD30 antigen by more than 75% of tumor cells[2]. It often occurs at a median age of 60, although it may occur at any age[3], and it is the second most common manifestation of cutaneous T-cell lymphoma[2]. The clinical course of C-ALCL is predominantly indolent, distinct from the systemic anaplastic large-cell lymphoma[3].

The rarity of primary C-ALCL justifies this case report, and the main goal is to emphasize the importance of considering this diagnosis as a possibility in large-cell cutaneous lymphomas. Therefore, the report presents the clinical identification of the lesion, anatomopathological findings, and a literature review on the theme, including pathophysiology, epidemiological aspects, clinical manifestations, and treatment.

Case report

Female, 58 years old, referred to the dermatology department after surgical resection of a nodular lesion with rapid growth on the right calf, performed 5 months earlier.

The pathology report indicated a malignant neoplasm of lymphoid/epithelioid atypical cells, ulcerated, infiltrating to the deep reticular dermis and hypodermis. Lateral and deep surgical margins were negative.

When the patient was examined, she presented new painful, violaceous papules, and nodules in the right lower limb (Fig. 1). Lymphadenopathy in the inguinal chain was absent. Thus, a biopsy of the new lesions was carried out, as well as an immunohistochemistry request for better diagnostic definition.

At a follow-up appointment 1 month later, the patient still had violaceous plaques on the right lower limb and no lymphadenopathy associated. The pathology reports were not available yet.

The patient was lost to follow-up and returned after approximately 1 year with the result of the immunohistochemical study of the first lesion resected from the right calf. The neoplasm was positive for CD45, CD30, and CD3 (Fig. 2). AE1AE3, S100, and CD20 antibodies, indicative of epithelial, melanocytic, and B-lymphoid lineage, were negative. The anaplastic lymphoma kinase (ALK) protein was also negative. The morphological features, combined with the immunohistochemical profile, revealed a CD30-positive lymphoproliferative disorder in the skin, consistent with C-ALCL.

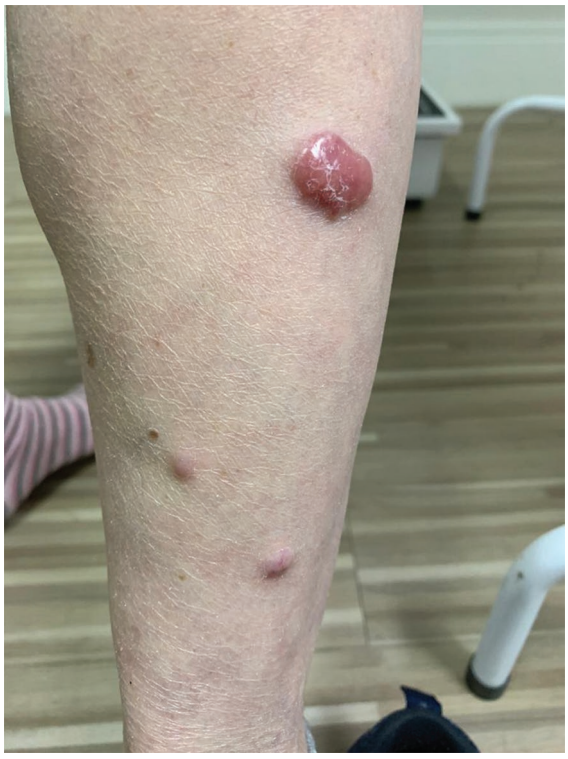

Figure 1. Large violaceous nodule in lower right limb, measuring 3.6 × 2.3 cm, accompanied by smaller papules below.

A positron emission tomography-computed tomography scan was performed, and no signs of systemic disease were found. The final diagnosis was primary C-ALCL.

Thus, the patient was referred to the hematology department. Radiotherapy was then administered for 4 weeks.

Lesions regressed but recurred about 1 year after treatment. The patient is currently undergoing a new cycle of radiotherapy.

Discussion

Primary cutaneous lymphomas are a heterogeneous group of non-Hodgkin lymphomas of the skin that does not have extracutaneous manifestations at the time of diagnosis. They mainly originate from T cells, even though they can also originate from B cells[4].

Approximately 6.4 million people worldwide are affected by primary cutaneous lymphomas[4]. The World

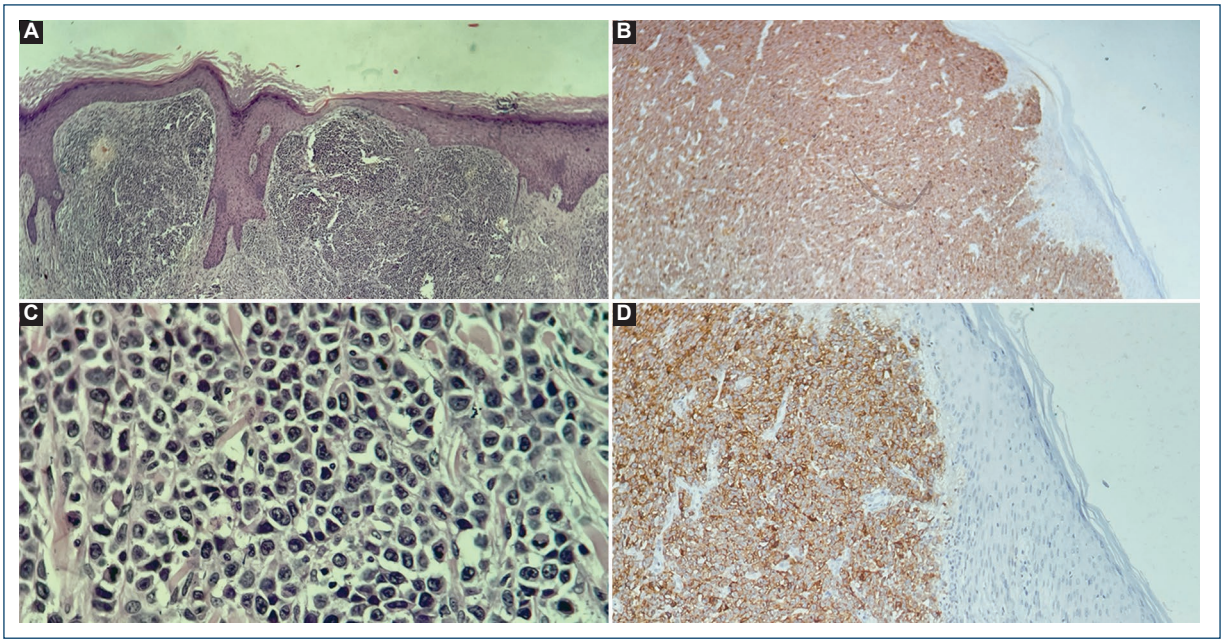

Figure 2. Histopathological and immunohistochemical (IHC) characteristics of skin neoplasm. **A:** panoramic view showing neoplasm infiltrating the dermis (×40, H&E). **B:** large cells with anaplastic features and mitosis in detail (×100, H&E). **C:** CD30 (×400, IHC). **D:** CD3 (×100, IHC).

Health Organization-European Organization for Research and Treatment of Cancer classification subdivides these types of lymphomas. According to this classification, among the subtypes of primary cutaneous lymphoma are primary cutaneous CD30+ lymphoproliferative disorders, in which CD30+ anaplastic large-cell lymphoma stands, also known as primary C-ALCL[2].

Anaplastic large-cell lymphoma is the second most common skin T-cell neoplasm after mycosis fungoides, accounting for approximately 30% of primary cutaneous lymphomas[5]. The group with the highest incidence is adults between 45 and 60 years old, with a slight predominance in males[6].

C-ALCL is mostly asymptomatic[3]. The presence of solitary papules or nodules, mainly located on the trunk or extremities, characterizes the disease[7]. These nodules persist for 3-4 weeks, tend to ulcerate over time, and show spontaneous regression (20-42% of cases) followed by relapses[5]. On average, 20% of patients present multifocal lesions, even though extracutaneous involvement rarely occurs[2].

Diagnosis occurs through clinical findings, laboratory tests, skin biopsy with anatomopathological analysis, and complementary immunohistochemical evaluation. At this stage, it is significant to ensure that in addition to positivity for CD30, negativity for ALK-1 is required to exclude the possibility of systemic ALCL with cutaneous involvement since this manifestation is more aggressive than C-ALCL[8].

Histological examination reveals a neoplastic proliferation of large lymphocytes in the dermis and subcutaneous cellular tissue. The epidermis is not usually involved, although epidermotropism is occasionally present[9]. The lymphocytes are of anaplastic appearance, with irregular and prominent nuclei, abundant cytoplasm, atypical mitoses, and some cells with plasmacytoid appearance[7].

The prognosis depends on multiple clinical and histopathological factors, with a median survival of 5 years in 97.5% of cases in the early stage[7]. Patients over 60 years old, absence of spontaneous regression, presence of extracutaneous dissemination, and extensive limb disease are related to an unfavorable prognosis[5].

As for treatment, it is mainly performed by local surgical excision. Radiotherapy is reserved for cancers with high tumor mutational burden and systemic chemotherapy is typically reserved for cases with a greater extent of disseminated disease[5].

In addition, when the lymphoma is refractory to main therapies, there is the possibility of performing autologous or allogeneic stem cell transplantation. However, due to the high morbidity and mortality associated with this therapy, it is reserved for stable patients with risk-benefit assessments[10].

Conclusion

Primary C-ALCL is an uncommon subtype of T-cell lymphoma. It is an exclusively cutaneous neoplasm and is distinguished by the presence of CD30-positive cells. Upon diagnosis of cutaneous ALCL, it is necessary to confirm the negativity for ALK-1 protein, to exclude the possibility of cutaneous manifestation of the systemic ALCL, which has worse prognosis.

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Conflicts of interest

None.

Ethical disclosures

Protection of individuals and animals. The authors state that for this investigation, no experiments were conducted on humans and/or animals.

Confidentiality of data. The authors declare to have followed their institution's protocols regarding the publication of patient data.

Right to privacy and written consent. The authors declare to have obtained written consent from patients and/or subjects mentioned in the article. The corresponding author must possess this document.

Use of artificial intelligence for generating texts. The authors declare that they did not use any type of generative artificial intelligence in drafting this manuscript, neither for the creation of figures, graphs, tables, and/or their respective captions.

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

Trichoscopic findings in folliculotropic mycosis fungoides: case report

Achados tricoscópicos na micose fungóide foliculotrópica: a propósito de um caso

Miguel Santos-Coelho[a], Joana A. Barbosa[b], and Ana L. João[c]*

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

ORCID: [a]0000-0002-2288-7306; [b]0000-0001-7351-5302; [c]0000-0002-2489-0138

Abstract

Folliculotropic mycosis fungoides (FMF) represents 10% of all mycosis fungoides cases and even though supraciliary lesions and alopecia are characteristic, there are few published papers documenting trichoscopic findings in these patients. We report the case of a 50-year-old man who presented to our department with FMF stage IB. Clinical findings included disseminated erythematous patches and plaques with a fine white-grayish scale, madarosis, and multifocal patchy alopecia of the scalp. Trichoscopy revealed a decreased number of pilosebaceous units, dilated follicular openings, black dots, vellus, and dystrophic hairs. Examination of the scalp presented widespread white scaling and areas with dotted and spermatozoa-like vessels. A revision of the literature showed that dilated follicular openings, black dots, and scale were less frequent findings in FMF, and dystrophic hairs were more common in advanced FMF. In the future, trichoscopic evaluation might guide differential diagnosis and define the threshold to biopsy lesions to identify early disease.

Keywords: Primary cutaneous T-cell lymphoma. Mycosis fungoides. Folliculotropic mycosis fungoides. Alopecia. Trichoscopy. Dermoscopy.

Resumo

A micose fungóide foliculotrópica (MFF) representa 10% dos casos de micose fungóide e, apesar das lesões supraciliares e alopecia serem características, os achados tricoscópicos destes doentes não se encontram bem definidos. Apresentamos o caso de um homem de 50 anos com MFF estádio IB, com múltiplas manchas e placas eritematosas com escama branco-acinzentada fina, madarose e alopecia multilocular do couro cabeludo. A triscoscopia revelou uma diminuição das unidades pilossebáceas, aberturas foliculares dilatadas, pontos negros e ainda cabelos velos e cabelos distróficos. A avaliação do couro cabeludo demonstrou escama esbranquiçada difusa e áreas com vasos punctiformes e vasos semelhantes a espermatozóides. A revisão da literatura mostrou que as aberturas foliculares dilatadas, pontos negros e a escama são achados relativamente incomuns e que os cabelos distróficos são mais comuns nas formas avançadas de MFF. No futuro, a tricoscopia poderá guiar o diagnóstico diferencial e definir o limiar de biópsia destes doentes.

Palavras-chave: Linfoma cutâneo primário de células T. Micose fungóide. Micose fungóide foliculotrópica. Alopecia. Tricoscopia. Dermatoscopia.

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

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Introduction

Mycosis fungoides (MF) is the most common type of cutaneous lymphoma and can be classified into distinct subtypes. Folliculotropic mycosis fungoides (FMF) is characterized by the folliculotropic infiltration of the epidermis by atypical T-cells, usually CD4+[1]. It represents 10% of all cases of MF[2], is more frequent in men, and usually diagnosed between 46 and 59 years of age[1].

The clinical manifestations of FMF are ample, making diagnosis a challenge. Because of this, delayed diagnosis is usual, ranging from 18 to 48 months after onset of symptoms[1,3], which is particularly concerning when considering that response to treatment is worse than classical MF and depends on staging.

Head and neck involvement is present in the majority of patients[1-3], and supraciliary lesions and alopecia are characteristic. These findings, associated with the histopathological presence of epidermal folliculotropic infiltration, make trichoscopic assessment of lesions appealing. Even so, there are few published papers documenting these trichoscopic findings.

Clinical case

We present the case of a 50-year-old man with a medical history of hepatitis B and C, medicated with tenofovir, who presented with a pruriginous disseminated dermatosis, affecting the head, neck, trunk, and limbs, characterized by erythematous patches and plaques with fine white-grayish scale, madarosis and multifocal patchy alopecia of the scalp (Fig. 1), and painless inguinal lymphadenopathies. Symptoms had started 1 year earlier and the first lesions appeared on the trunk.

Trichoscopy of the scalp (Fig. 2) revealed a decreased number of pilosebaceous units, with several dilated follicular openings (some with milky-white globules) with perifollicular accentuation, black dots, and some vellus hair and dystrophic hairs. White scaling in a widespread distribution, areas with dotted vessels, and spermatozoa-like vessels was also noted.

Hair and skin biopsies were compatible with FMF. Laboratory and imaging workup associated with lymph node biopsy led to a pT2bN0M0-IB staging. The patient was treated with acitretin and electron bath therapy and later with bexarotene and brentuximab. He later died of MRSA septic shock.

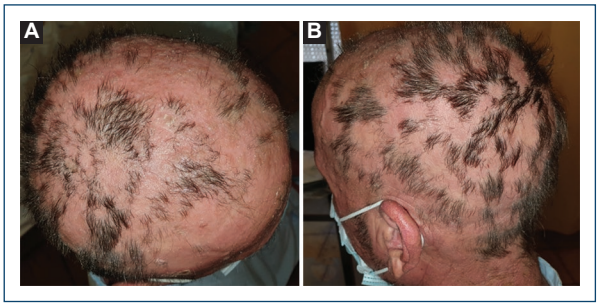

Figure 1. A and B: multifocal patchy alopecia and scaling of the scalp.

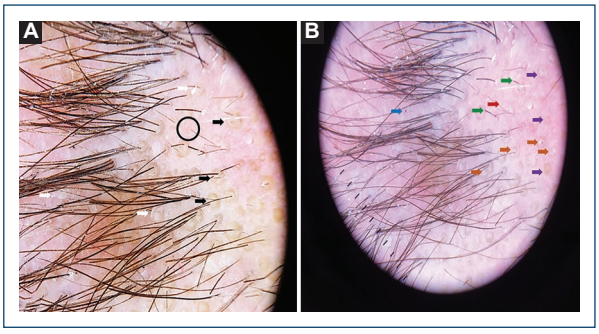

Figure 2. A: dilated follicular openings/yellow dots (black arrow), white scaling (white arrow), dotted vessels (black circle). **B**: decreased number of pilosebaceous units, milky white-globules (orange arrow), perifollicular accentuation (purple arrow), dystrophic hairs (green arrow), black dots (blue arrow), spermatozoa-like vessels (red arrow).

Discussion

Trichoscopy is an easy-to-use and non-invasive technique that allows the evaluation of the scalp and hair. At present, there is a lack of published data detailing these findings in FMF.

Sławińska et al.[2] published a systematic review detailing the dermoscopic and trichoscopic findings of cutaneous lymphomas, including FMF. In MF, dermoscopy can reveal spermatozoa-like vessels (first described by Lallas et al.[4]), which seem to be a somewhat specific finding[2]. This type of vessel was also present in our patient and is thought to represent the proliferation of vascular cells in dermal papillae (translating, in dermoscopy and trichoscopy, into a round shape) and through the underlying dermis (corresponding to the linear portion of the vessels)[5].

Gallo et al. published the biggest series of trichoscopic findings in FMF patients with scalp involvment[6].

This series of 18 patients, three of which with stage IB as our patient, and most with patchy-plaque alopecia, showed, in the majority of cases, a decreased number of pilosebaceous units, yellow dots, dystrophic hairs, vellus hair, dotted vessels, and spermatozoa-like vessels[6]. These findings translate follicular changes related to folliculotropic infiltration of atypical T-cells with disruption of the normal follicular cycle. Black dots and scale, which were readily identified in our patient, were less frequent findings[6].

Gallo et al. also presented a subgroup analysis comparing findings in generalized alopecia and patchy-plaque alopecia, and in early stage and advanced FMF. Scale was more common in patchy alopecia (but statistical significance was not met)[6]; this was, indeed, a prominent finding in our patient. On the other hand, broken (dystrophic) hairs were more common in advanced FMF, but not exclusive to this subgroup[6]. Accordingly, we found dystrophic hairs in our patient, which probably relates to the fact that FMF (and MF in a broader sense) is an asymmetrical pathophysiological processes that manifest, in the same patient, with lesions in different stages of its natural story.

The coexistence of several different (and often unspecific) trichoscopic findings in FMF contributes to the difficulty of standardizing the examination of these patients. When considering isolated trichoscopic findings, differential diagnosis is extensive: yellow dots are present in alopecia areata and discoid lupus erythematosus; dystrophic hairs are commonly found in trichotillomania and tinea capitis; and white scaling can be found in different forms of eczema, dermatomyositis, and even pityriasis rubra pilaris. To consider FMF, one should take into account the constellation of supporting findings in trichoscopy and correlate them with clinical and histopathological aspects. Regarding the later, trichoscopy can also be useful by guiding biopsy site selection, as perifollicular accentuation reflects folliculotropism in histopathological examination[7].

At this time, more data regarding the trichoscopic examination of FMF patients is needed; clinical algorithms based on larger series of patients and reports of findings in individual cases will contribute to help guide differential diagnosis and define the threshold to biopsy lesions, as early identification and treatment of these patients is of the utmost importance.

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Conflicts of interest

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Ethical disclosures

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DERMATOLOGY IMAGES

A rare case of granulomatous slack skin with scarce multinucleated giant cells

Um raro caso de cútis laxa granulomatosa com escassas células gigantes multinucleadas

Laísa E. de Hollanda[1a], Carolina S. de Oliveira[1], Isabella C. Mendes-Alexandre[1], Rebeca de O. Alves-Melo-Martins[1], Vanessa R. Ferreira[1], Monique F. dos Reis[2], Silvana de A. Damasceno-Ferreira[3], and Luciana M. dos Santos[1]

[1]Department of Dermatology, Hospital Universitário Getúlio Vargas; [2]Department of Pathology, Hospital Universitário Getúlio Vargas; [3]Department of Pathology, Fundação Hospitalar de Dermatologia Tropical e Venereologia Alfredo da Matta. Manaus, AM, Brasil
ORCID: [a]0000-0003-4240-0777

A previously healthy 23-year-old woman was observed with erythematous and infiltrated plaques associated with significant skin flaccidity forming a pendulous skin fold in the right armpit and a brown macular pigmentation with mild skin flaccidity in the left armpit (Fig. 1). Lesions were asymptomatic and had a 2-year evolution.

A skin biopsy of the right armpit revealed a dense dermal granulomatous infiltrate of atypical lymphocytes, neutrophils, histiocytes, plasma cells, eosinophils, and scarce multinucleated giant cells (Figs. 2A-C). Verhoeff staining demonstrated a marked reduction of elastic fibers (Fig. 2D). Immunohistochemistry of the dermal infiltrate showed positivity for cluster of differentiation (CD) 3 and 4 (Fig. 3) and loss of CD7 and CD8 expression, findings that are compatible with the diagnosis of granulomatous slack skin (GSS).

GSS is a rare variant of mycosis fungoides that mainly affect caucasian men between the third and fifth decades of life[1,2].

Histology shows, in addition to elastophagocytosis and emperipolesis, a granulomatous infiltrate mainly composed by atypical lymphocytes, macrophages, and

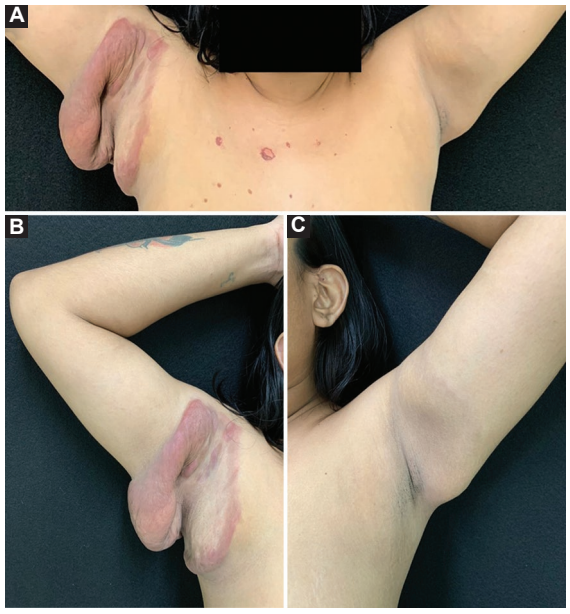

Figure 1. A: skin lesions in both armpits with a 2-year evolution. **B:** erythematous and infiltrated plaques associated with significant skin flaccidity in the right armpit. **C:** brown macular pigmentation with mild skin flaccidity in the left armpit.

***Correspondence:**
Laísa E. de Hollanda
E-mail: laisahollanda@gmail.com

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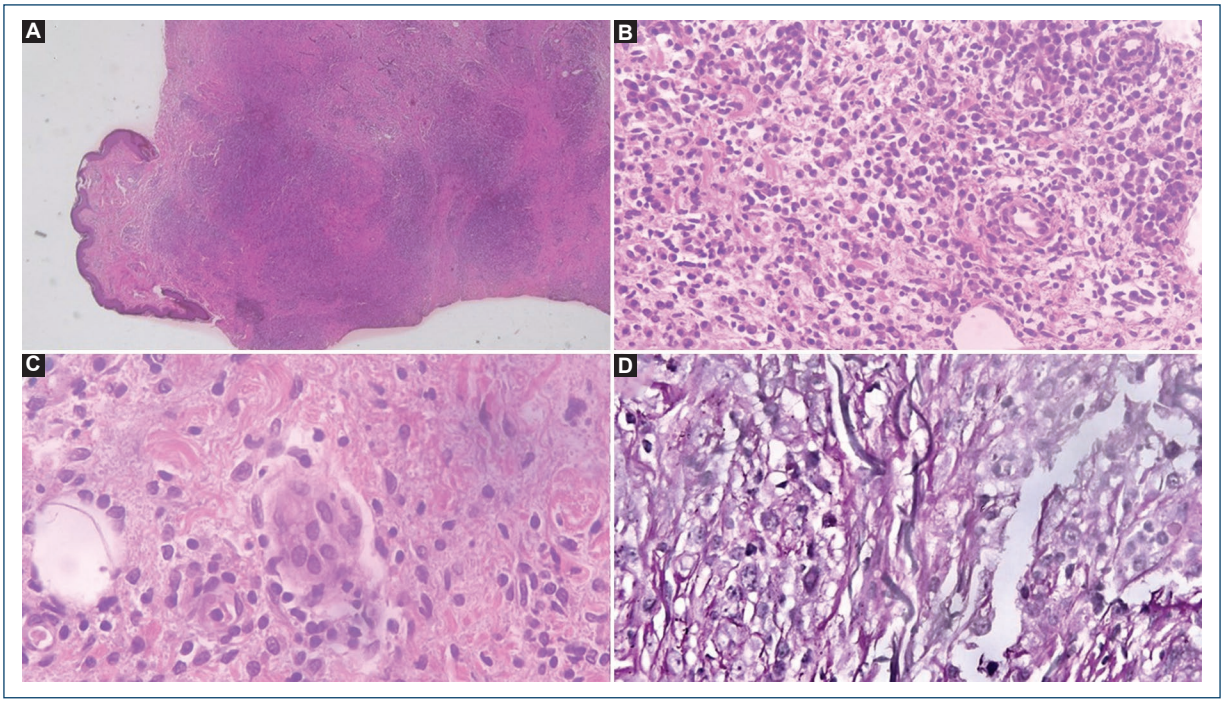

Figure 2. Hematoxylin-eosin-stained sections at ×40, ×200 and ×400, respectively. **A:** dense granulomatous infiltrate affecting the entire dermis and subcutaneous tissue. **B:** atypical lymphocytes, neutrophils, histiocytes, plasma cells, eosinophils composing the granuloma. **C:** scarce multinucleated giant cells. **D:** verhoeff-stained section at ×600; reduction of elastic fibers.

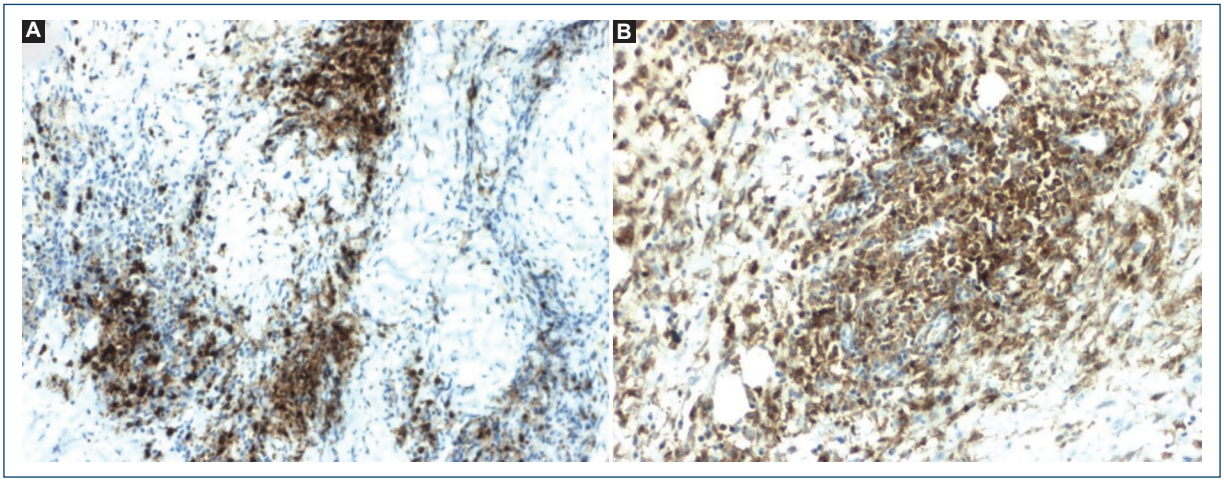

Figure 3. Immunohistochemistry showing atypical cells expressing: **A:** CD3+; **B:** CD4+.

multinucleated giant cells with 20-30 nuclei[1-3]. This last aspect was not found in our patient and to the best of our knowledge, only another similar case has been reported[4]. Regarding immunohistochemistry, it demonstrates a cell with a T-helper immunophenotype[1], as in the present case, with monoclonal rearrangement of T-cell receptor genes in most tested patients[1,2]. In addition, some subpopulations of macrophages secrete metalloproteinases that are considered responsible for the degradation and remodeling of the dermal tissue[3].

Furthermore, other lymphoproliferative disorders may be present in up to 50% of cases, so patients must be

screened and followed up[1,2]. Due to its rarity, there is no standard treatment, and a complete remission of the disease has seldom been reported[4-6].

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Conflicts of interest

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DERMATOLOGY IMAGES

A case of Becker's melanosis on the forehead: a rare presentation

Um caso de melanose de Becker na fronte: uma apresentação rara

Dilek Menteşoğlu

Department of Dermatology and Venereology, Acıbadem Eskişehir Hospital, Eskişehir, Turkey
ORCID: 0000-0002-5438-0526

A previously healthy 23-year-old male patient presented with a brown spot on his forehead, first noticed at the age of 13, with no reported changes in the previous years. A sharply well-circumscribed 60 × 30 mm light brown patch on the right forehead with no hypertrichosis was noted (Fig. 1A). There was no firmness, palpable mass, or tenderness on palpation. Dermoscopy revealed a homogeneous melanocytic lesion with a faint reticular pattern and perifollicular hypopigmentation (Figs. 1B and 1C). Histopathological examination showed acanthosis and increased pigmentation in the basal layer of the epidermis. Based on clinical, dermoscopic, and histological findings, Becker's melanosis was diagnosed. Laser therapy was offered; however, the patient refused. Becker's melanosis, also known as Becker's nevus, is a relatively common benign cutaneous hamartoma with epidermal or dermal elements[1]. It is clinically characterized by well-circumscribed, unilateral, acquired hyperpigmentation, usually first noticed around puberty and more prevalent in males[2]. Although it is most frequently seen in the shoulder, scapular area, and upper extremity, it can be seen anywhere[2]. When Becker melanosis is referred to as Becker nevus syndrome, it may occasionally be linked to developmental abnormalities like ipsilateral breast hypoplasia, extra nipples, aplasia of the pectoralis major muscle, and other musculoskeletal and spine abnormalities[3]. The differential diagnosis of Becker melanosis includes congenital melanocytic nevus, congenital smooth muscle hamartoma, plexiform neurofibroma, post-inflammatory hyperpigmentation, and café-au-lait macules[2,4]. Diagnosis is mainly clinical; however, a skin biopsy can be helpful to support the diagnosis of Becker's melanosis, mainly when dealing with atypical presentations.

Facial Becker nevus is not widespread and hypertrichosis does not always accompany it. There is a need for larger studies on whether this case is associated with any anomaly and its prevalence. The purpose of reporting our case is to remind and emphasize that Becker's nevus may be outside of the usual areas and should be kept in mind in the differential diagnosis of hyperpigmented, sharply demarcated spots on the face.

Correspondence:
Dilek Menteşoğlu
E-mail: drdilek.2013@gmail.com

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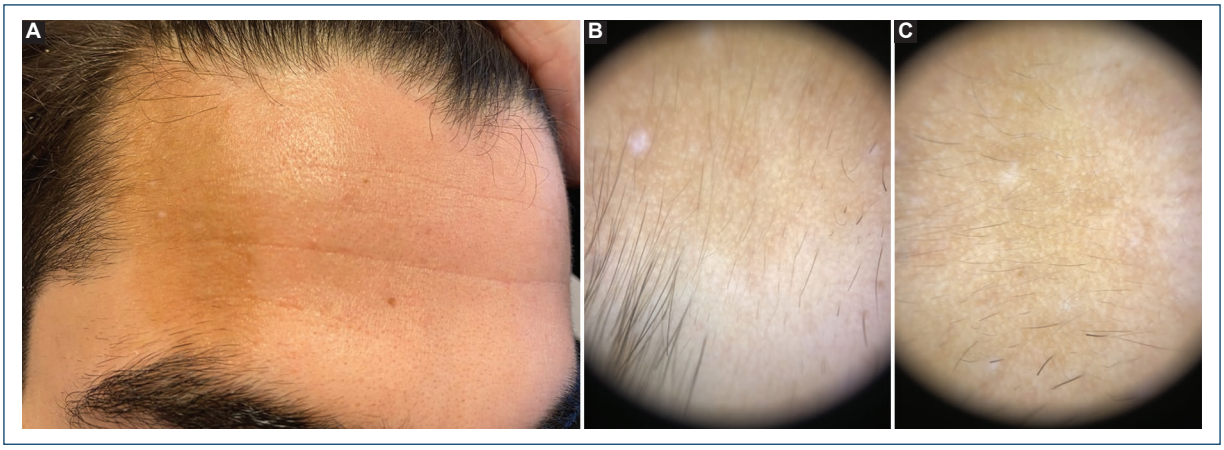

Figure 1. A: a sharply circumscribed 60 × 30 mm light brown patch on the right forehead. **B and C:** dermoscopy (dermlite DL4 polarized mode) showed a faint reticular pattern of pigmentation, perifollicular hypopigmentation, and a sharply demarcated unstructured white area (biopsy site).

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Conflicts of interest

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DERMATOLOGY IMAGES

Radiation-induced morphea: an uncommon entity

Morfeia pós-irradiação: uma entidade rara

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

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

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

A 70-year-old man presented to the dermatology department with a slowly growing, asymptomatic, indurated 10 × 8 cm plaque, with a central white area and erythematous borders, of the right dorsal area (Fig. 1). Seventeen years earlier, the patient had developed a primary cutaneous follicle center lymphoma of the same region and had undergone treatment with 25 sessions of radiotherapy, with a complete response and no recurrence. Before this, no significant atrophy or radiodermatitis was noted.

Histopathology from a punch biopsy revealed no epidermal changes, a marked thickening of collagen fibers, with a dense, mainly perivascular and periadnexal, lymphohistiocytic infiltrate of the reticular dermis and hypodermis (Fig. 2). Perieccrine fat substitution by fibrosis was also present. These findings supported the diagnosis of radiation-induced morphea (RIM). The patient started topical betamethasone with gradual improvement over the next few months.

RIM is a rare entity most commonly associated with radiotherapy following breast cancer[1]. Most cases develop in the months following treatment, but a latent period of several years has been described[2,3].

The precise pathophysiological mechanisms leading to RIM have not been established, but increased transforming growth factor-β signaling is thought to be a key element in inducing extracellular matrix deposition and extensive fibrosis[2].

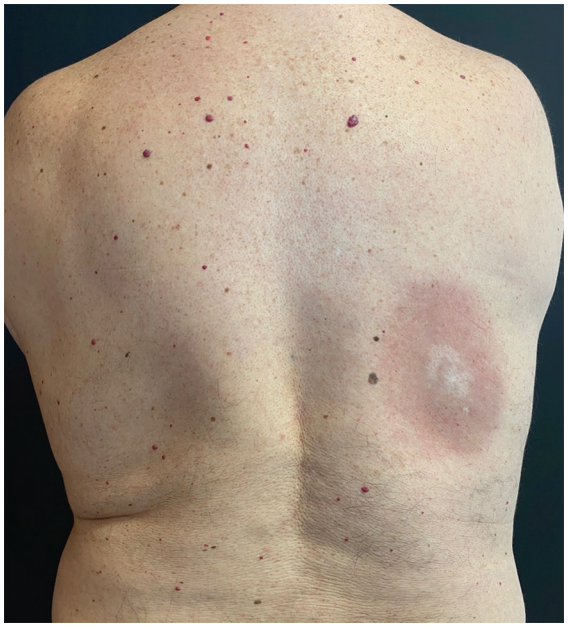

Figure 1. Indurated plaque of the right dorsal area.

Differential diagnosis is vast and includes chronic radiation dermatitis, radiation recall dermatitis, and

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

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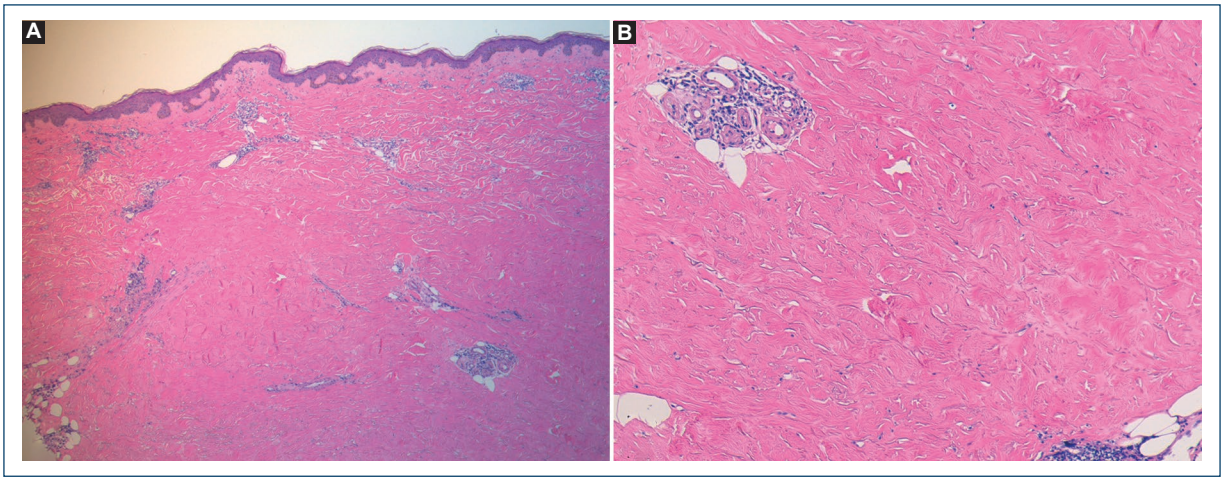

Figure 2. Punch biopsy revealing marked thickening of collagen fibers and a dense dermal perivascular and periadnexal lymphohistiocytic infiltrate (**A:** H and E, ×40; **B:** H and E, ×100).

tumor recurrence, making skin biopsy an important step in these patients' evaluation.

Treatment is difficult and includes potent and superpotent topical corticosteroids, topical calcineurin inhibitors, oral methotrexate, oral corticosteroids, and phototherapy.

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Conflicts of interest

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Ethical disclosures

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