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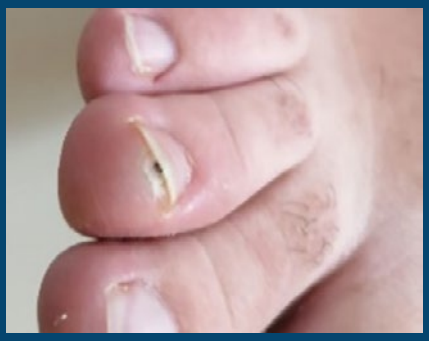

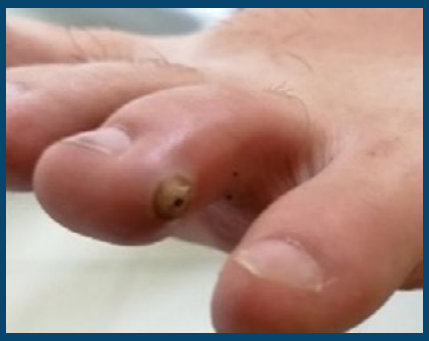

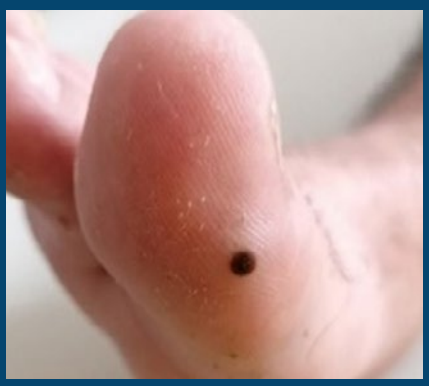

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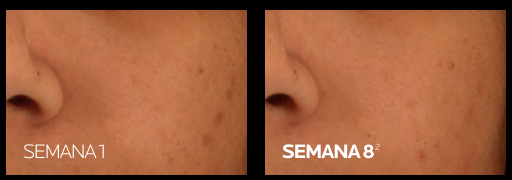

VISUALIZAÇÃO EM 3D DA MELANINA NA PELE[3]

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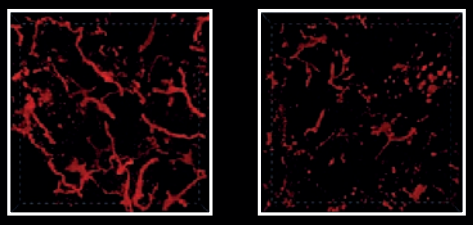

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REVIEW ARTICLE

Atopic dermatitis and vitamin D

Dermatite atópica e vitamina D

Inês Rodrigues[1] and Margarida Gonçalo[1,2]*

[1]Faculdade de Medicina, Universidade de Coimbra; [2]Serviço de Dermatologia, Coimbra University Hospital, Coimbra Local Health Unit. Coimbra, Portugal

Abstract

Atopic dermatitis (AD) results from the interaction between dysfunction of the skin barrier, dysregulation of the immune system, and alteration of the skin microbiome. As the most common inflammatory skin disease worldwide and still increasing, it is a real health problem. Vitamin D deficiency is also considered a global problem affecting 13 out of 100 people in Europe. Since vitamin D is involved in the formation of the epidermal barrier, by the synthesis of structural proteins and regulation of keratinocyte proliferation and differentiation, there is a rational to evaluate the relation between vitamin D levels and the prevention or treatment of AD. The authors performed a review of the existing scientific literature on the role of vitamin D in AD. Although studies are scarce not very robust with no consensual results, most studies report lower serum levels of vitamin D in patients with AD. In addition, there seems to be an inverse relationship between plasma levels of vitamin D and clinical severity, a hypothesis that is reinforced by studies that demonstrated a statistically significant benefit of vitamin D supplementation for improving clinical symptoms and signs of AD. Some studies also suggest a possible influence of prenatal vitamin D levels on the onset of AD during childhood. Therefore, vitamin D supplementation may play a relevant role as a complement to the treatment of AD or for its prevention, but more and better scientific evidence is needed to confirm this.

Keywords: Atopic dermatitis. Vitamin D. Vitamin D deficiency. Skin.

Resumo

A dermatite atópica resulta da interação entre a disfunção da barreira cutânea, a desregulação do sistema imunitário e a alteração do microbioma da pele. Sendo a doença inflamatória da pele mais comum a nível mundial e com incidência crescente é um verdadeiro problema de saúde. O défice de vitamina D é também um problema de saúde global, que afeta cerca de 13 em cada 100 cidadãos europeus. Uma vez que a vitamina D está envolvida na formação da barreira epidérmica, pela síntese de proteínas estruturais e pela regulação da proliferação e diferenciação dos queratinócitos, é expectável que os níveis séricos de vitamina D possam ter um papel na prevenção e/ou no tratamento da dermatite atópica. Neste artigo de revisão narrativa foi revista a literatura científica existente sobre o papel da vitamina D na dermatite atópica. Apesar de escassos, pouco robustos e não consensuais, a maioria dos estudos relatam níveis séricos de vitamina D mais baixos em doentes com dermatite atópica, com uma relação inversa entre os valores plasmáticos da vitamina e a gravidade da doença, hipótese reforçada por estudos que demonstraram uma relação estatisticamente significativa entre a suplementação e a melhoria dos sintomas e sinais clínicos. Existem também evidências que sugerem uma possível influência de valores pré-natais de vitamina D

***Correspondence:**
Inês Rodrigues
E-mail: ivprodrigues99@gmail.com

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no surgimento de dermatite atópica durante a infância. Desta forma, a suplementação com vitamina D poderá ter um papel relevante como complemento do tratamento da dermatite atópica, mas são necessárias mais e melhores evidências científicas para o comprovar.

Palavras-chave: Dermatite atópica. Vitamina D. Deficiência de vitamina D. Pele.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease with increasing incidence, affecting nearly 15-20% of children and up to 10% of adults worldwide[1,2]. It is characterized by eczema and itching[3], with a complex and not fully understood pathophysiology influenced by genetic and environmental factors, involving the interaction between an inappropriate immune response, skin barrier dysfunction, and alteration of the skin microbiome[4].

The treatment goal in AD is to reduce skin inflammation, and disease management is based on the use of emollients, topical corticosteroids calcineurin inhibitors, and, in severe cases, also systemic immunomodulators[5,6]. Treatment allows a decrease in severity and exacerbations but there is no cure and its signs and symptoms have a negative impact on the patient's quality of life[7].

Vitamin D, classically known for its role in bone metabolism and calcium homeostasis, is a steroid hormone with several extraosseous actions. This vitamin is mainly obtained from the skin through the action of ultraviolet B (UVB) radiation, through the conversion of 7-dehydrocholesterol (7-DHC) into vitamin D3, but also through food or supplementation[8,9].

The full consequences of vitamin D deficiency at cutaneous and immunological levels are not yet known. A possible relationship between vitamin D and the development of allergic diseases emerged when an increased incidence of allergic diseases was noticed at higher latitudes, where vitamin D deficiency is more common[10].

Some studies have shown that lower serum levels of vitamin D are related with more severe AD presentations and that vitamin D supplementation may be an effective treatment for AD[3,11,12]. Furthermore, as several data support the involvement of vitamin D on several aspects of the pathogenesis of AD, namely, on epidermal barrier dysfunction and dysregulation of the immune system[8,10], a relationship between vitamin D levels and the risk and severity of AD has been hypothesized.

Objectives

This work aims to review existing scientific literature on the relationship between vitamin D levels and AD, after performing a review on vitamin D and its metabolism.

Vitamin D metabolism

Vitamin D is a fat-soluble vitamin that exists in two forms: vitamin D3 (cholecalciferol), produced in the skin or obtained from the diet, and vitamin D2 (ergocalciferol), obtained from the diet. Few foods naturally contain vitamin D (oily fish, cod liver oil, egg yolk, shiitake mushrooms, liver), so its synthesis in the skin is the principal way to obtain vitamin D, responsible for 90% of vitamin D replacement[10,13].

Pre-vitamin D3 is synthesized in the epidermis from 7-DHC, an intermediate in the synthesis of cholesterol, by the action of UVB radiation (290-315 nm). It is then converted into vitamin D3 through a temperature-dependent reaction[13-15].

Vitamin D, whether obtained through the diet or through skin synthesis, is biologically inactive and requires two hydroxylation reactions to become active. The first occurs in the liver, by the enzyme 25-hydroxylase, to form calcidiol (25(OH)D), the main circulating form of vitamin D, which has a half-life of 2-3 weeks. It then goes through hydroxylation again by the enzyme 1α-hydroxylase, in the kidney, to be converted into calcitriol ($1,25(OH)_2D$), the most active form and which has a half-life of 4-6 h. This process depends on parathyroid hormone (PTH), serum phosphate values, and growth hormone. The enzyme 1α-hydroxylase is expressed in extra-renal organs, so the second hydroxylation of vitamin D may happen in extra-renal locations such as alveolar macrophages, osteoblasts, lymph nodes, placenta, colon, breast, and keratinocytes, suggesting an autocrine-paracrine action of calcitriol[14,16,17].

Calcium homeostasis is the most important function of vitamin D. When calcium receptors of the parathyroid glands detect low levels of ionized calcium, the gland increases the secretion of PTH, which will stimulate the renal production of calcitriol from circulating calcidiol, and enhance calcium transport at intestinal, bone, and renal levels. PTH secretion will decrease when serum calcium values return to normal. Therefore, normal serum calcidiol values are important to guarantee calcitriol synthesis and, consequently, a normal plasma calcium level. Vitamin D deficiency results in low levels of calcidiol, and, consequently, a decrease in calcitriol synthesis and calcium absorption, and an increase in PTH levels[13,14,18].

Vitamin D deficiency

Insufficient amounts of circulating vitamin D constitute a global health issue. In Europe, the prevalence rates of vitamin D deficiency are alarming and require measures both from a public health and clinical point of view. Although vitamin D levels may vary depending on the age group, ethnicity, and latitude of the study population, 13 out of every 100 European citizens have serum 25(OH)D concentrations lower than 30 nmol/L (12 ng/mL)[16,19,20].

The best indicator of vitamin D status in the body is the serum 25(OH)D concentration, which reflects the free fractions of vitamin D metabolites but there is no consensus regarding an optimal value among different scientific societies and institutions[16,18].

According to the recommendations of the global consensus on the prevention and guidance of nutritional rickets from 2016, serum 25(OH)D values lower than 30 ng/mL indicate vitamin D deficiency[21]. The American academy of pediatrics has postulated values of 25(OH) D levels > 20 ng/mL as sufficient, while the pediatric endocrine society has defined 25(OH)D levels below 30 ng/mL as insufficiency and below 20 ng/mL as deficiency[18].

In Portugal, Direção-Geral da Saúde issued a clinical guideline on the "Prevention and Treatment of Vitamin D Deficiency" (Prevenção e Tratamento da Deficiência de vitamin D), establishing similar plasma concentration values of 25(OH)D that define vitamin D insufficiency or deficiency, in adults and children[22].

Vitamin D and skin physiology

Keratinocytes are the only cells in the body capable of synthesizing vitamin D from 7-DHC. They express vitamin D receptors (VDR) that respond to the active form of vitamin D, which, along with calcium, is one of the main regulators of epidermal differentiation. Vitamin D has a dose-dependent effect on keratinocyte proliferation and differentiation: at low concentrations it increases keratinocyte proliferation, whereas at high concentrations it reduces keratinocyte proliferation and promotes their differentiation by increasing the expression of structural components of the cornified envelope and the synthesis of ceramides, which potentiate the pro-differentiating effect of calcitriol on keratinocytes (feedback loop)[13,14,23,24].

Differentiation of epidermal cells, specifically the keratinocytes, is mediated by vitamin D through the VDR. It is a sequential process that requires the selective binding of the VDR to two main coactivators: the VDR-interacting proteins (DRIP) and the receptor coactivators steroids (SRC). DRIP selectively binds to VDRs and is predominantly expressed during keratinocyte proliferation. As cells differentiate, DRIP expression decreases and SRC expression increases, and VDR begin binding to SRC[13,15,23].

Vitamin D and skin's immune system

The skin's innate immune system is constituted by immune cells (such as neutrophils, monocytes, macrophages, natural killer cells, and innate lymphoid cells), the physical barrier, and antimicrobial peptides (AMPs)[14]. The presence of VDR in different cells of the immune system demonstrates the importance of vitamin D in their regulation[24,25], namely in keratinocyte expression of proinflammatory cytokines.

Calcitriol modifies the function of adaptive immune cells: it suppresses the maturation of dendritic cells (DC), inhibits the secretion of Th1 and Th17 proinflammatory cytokines, and promotes the production of Th2 cytokines. In addition, it induces the production of Treg cells, CD4+ and CD25+, which suppress proinflammatory responses from other immune cells and prevent exaggerated or autoimmune responses[8,13,24,25].

Monocytes and other antigen-presenting cells, such as DC, are important targets of the immunomodulatory effects of vitamin D. Calcitriol modifies the maturation and differentiation of DC, giving them a more adherent spindle cell morphology and a less mature and more immunologically tolerant phenotype, both in the production of cytokines and surface markers, therefore decreasing the activation of adaptive immunity[18,24,25].

Vitamin D plays a significant role in the defense against opportunistic infections, by directly activating the production of AMPs, such as cathelicidin and beta-defensin, and stimulating the synthesis of proteins that contribute to the integrity of the epidermal barrier, such as filaggrin[14,19,23,25].

The role of vitamin D in AD

AD patients have skin barrier disruption and dysregulation of the innate immune system, which leads to inappropriate responses to allergens and microbial pathogens[3]. As previously mentioned, vitamin D promotes the differentiation of keratinocytes, stimulates the synthesis of structural components of the epidermal barrier, and increases the expression of AMPs. Therefore, low serum concentrations of vitamin D can lead to a defective epidermal barrier and immunological

changes that may contribute to AD worsening[3,14,19]. Nevertheless, contrary to psoriasis, topical use of vitamin D has not shown to be successful in AD.

More than 90% of vitamin D in the body is synthesized in keratinocytes by UVB radiation. Variables such as season, latitude, and air pollution can significantly alter vitamin D levels, as can direct sun exposure, skin phototype, lifestyle, and cultural factors (type of clothing)[10]. Geographic areas with less UVB exposure have a higher prevalence of AD and it has been found that there is a relationship between the onset and/or worsening of AD and winter. Furthermore, UV phototherapy is one of the treatment options for moderate to severe AD. Therefore, seasonal factors such as climate, UVB radiation, and vitamin D status are expected to influence the clinical course of AD[9,11,26].

VDR gene, located on the long arm of chromosome 12, has polymorphisms in various diseases which may influence vitamin D function. Some of these VDR polymorphisms influence the severity and susceptibility of AD, as confirmed by the identification of a polymorphism present in patients with severe AD, therefore indicating that VDR and vitamin D may contribute to AD control[14,15,27-29].

Low vitamin D serum levels in AD

Different studies have identified decreased serum levels of 25(OH)D in patients with inflammatory skin diseases, specifically AD, comparatively to healthy people[3,28,30].

A systematic review by Kim et al. selected seven observational studies to infer a possible relationship between serum 25(OH)D levels and AD which included in total of 986 AD patients and 657 healthy controls. One study included only adults, four studies included only children, and two included patients of all ages. The AD group had lower serum 25(OH)D values than the control group, if patients of all ages were included, especially in the subgroup with pediatric patients ($p = 0.0006$) but not in the adult subgroup ($p = 0.50$). However, the studies were considered statistically heterogeneous ($I2 = 98\%$)[3].

Fu et al. conducted a meta-analysis of 22 studies, which concluded that serum 25(OH)D levels in children with AD were significantly lower than in the healthy control group ($p = 0.001$), and values in patients with mild disease were significantly higher compared to patients with severe disease, according to SCORAD ($p < 0.001$)[31].

A study by Lipińska-Opałka et al. showed that vitamin D deficiency was significantly more frequent in children with allergic diseases, AD and asthma than in the control group ($p = 0.007$) and, again, serum vitamin D values were statistically higher in the group of children with mild compared to severe disease ($p = 0.03$)[32].

A small cross-sectional study carried out by Barlianto et al. investigated a possible association between serum vitamin D values, cytokine profile, and AD severity in 36 children aged up to 12 months, 19 with mild and 17 moderate disease, according to SCORAD. There was a high prevalence of vitamin D deficiency and insufficiency in children with AD with mean 25(OH) D values significantly lower in patients with moderate disease compared to mild disease ($p = 0.001$)[33].

Prenatal vitamin D serum levels and AD in childhood

Since 25(OH)D crosses the placenta, maternal 25(OH) D serum levels are the best indicator of the level of exposure of the fetus to vitamin D, so an insufficient value in the mother translates into an insufficient value in the fetus. Low levels of 25(OH)D during pregnancy are associated not only with complications in maternal and fetal health but also in the neonatal period and during childhood. Vitamin D is important for lung maturation and fetal immunity development. Thus, altered values of vitamin D may have a causal relationship with the development of allergic diseases in childhood[10,34,35].

Nevertheless, studies attempting to show a causal relationship between fetal exposure to vitamin D in utero and the development of AD in childhood obtained contradictory results.

Palmer et al. evaluated the influence of vitamin D levels in the umbilical cord on the development of allergic diseases in 270 children and concluded that the risk of eczema at 1 year decreased as 25(OH)D values increased: a 10 nmol/L increase in 25(OH)D concentration was associated with a 12% decrease in risk ($p = 0.002$). Cumulative incidence at 3 years old also showed a significant association with 25(OH)D values: an increase of 10 nmol/L reduced risk by 8% ($p = 0.005$)[36].

In a prospective cohort study by Baïz et al., a significant association was found between 25(OH)D values in the umbilical cord and the risk of developing AD at 1 ($p = 0.05$), 3 ($p = 0.02$) and 5 years old ($p = 0.005$). However, no significant association was found at 2 years old[37].

Another prospective cohort study of 288 pregnant women, carried out by Smith et al., identified a

significant association between maternal 25(OH)D values in early pregnancy and risk of atopy at 2 years old: children whose mothers had 25(OH)D values lower than 30 nmol/L at 13 weeks of pregnancy had a significantly higher risk of developing AD at 2 years than children of mothers with values above 50 nmol/L ($p < 0.05$)[35].

El-Heis et al. performed a double-blind randomized trial to study the effect of vitamin D supplementation (cholecalciferol 1000 IU/day) from 14 weeks until the end of pregnancy on the development of AD at different pediatric ages. Children in the supplementation group had an odds ratio of developing AD at 1, 2, and 4 years lower than those in the placebo group, although the difference was not statistically significant. No association was identified between serum 25(OH)D values during pregnancy and the development of AD in children, at any age. However, although no statistically significant, a relationship was found between supplementation and breastfeeding duration: the risk of AD at 12 months was reduced in the group of children that were breastfed for more than 1 month ($p = 0.03$), compared to those that were breastfed for > 1 month ($p = 0.66$), suggesting protective effect of supplementation with increasing the concentration of cholecalciferol in breast milk[38].

Although several studies indicate a negative association between maternal 25(OH)D values during pregnancy and the development of AD at an early age, other studies have not identified a significant relationship[39,40]. A meta-analysis combining seven randomized controlled trials to investigate a possible association between vitamin D supplementation in pregnant women or children and the development of allergic diseases, including AD in five of these studies, found no statistically significant differences, even though the length of follow-up and the dose of supplementation varied[39].

Shimizu et al. in a prospective cohort study intended to describe risk factors for the development of AD in the 1st year of life, found no association with vitamin D levels during pregnancy or at delivery or prenatal and postnatal vitamin D supplementation[40].

Vitamin D supplementation in the treatment of AD

Vitamin D supplementation is the most used strategy to restore vitamin status[16]. The efficiency of vitamin D supplementation in decreasing AD severity and improving its symptoms and clinical signs has been shown in some studies but is not consensual.

A systematic review and meta-analysis carried out in China with 32 randomized controlled trials and 2347 pediatric patients concluded that supplementation significantly reduced SCORAD and EASI in children with AD compared to the control group ($p = 0.009$)[41].

Imoto et al. carried out a prospective study including 152 AD children, 116 (76.3%) with insufficient or deficient plasma concentrations of 25(OH)D. During the first 4 weeks, the vitamin D deficiency group received 50 IU/week and the insufficiency group received 15 IU/week, after which all patients received a maintenance dose of 15 IU/week during the next 2 months. After 3 months, vitamin D values were significantly higher ($p < 0.001$), SCORAD was reduced ($p < 0.001$) and bacterial infections were less common in the group with improvement after supplementation ($p = 0.01$)[42].

In a double-blind, placebo-controlled study for 12 weeks in 86 children with severe AD treated with topical corticosteroid (1% hydrocortisone cream, twice a day), randomized 1:1 to receive cholecalciferol (1600 IU/day or placebo), the experimental group achieved significantly higher plasma 25(OH)D values compared to the control group ($p < 0.001$) and the mean EASI score was significantly lower than in the placebo group ($p = 0.035$)[43].

Four randomized, double-blind, placebo-controlled studies with no statistical heterogeneity between studies ($I^2 < 50\%$) gathered to perform a meta-analysis concluded that both EASI and SCORAD significantly decreased after vitamin D supplementation ($p < 0.00001$)[3].

As vitamin D regulates the production of AMPs, through induction of cathelicidin expression in keratinocytes[8,10,12], Albenali et al. evaluated the clinical severity and cathelicidin LL-37 levels in patients with AD after 2 months of vitamin D supplementation. Concurrent with a 42% SCORAD reduction ($p < 0.001$) there was a significant increase in LL-37 levels, both in lesioned and non-lesioned skin ($p = 0.0004$). This study also reinforced the correlation between AD severity and low LL-37 levels ($p = 0.01$), and suggested that vitamin D deficiency can lead to a decreased antimicrobial defence and, consequently, increased AD severity due to enhancing *Staphylococcus aureus* colonization[44]. SCORAD and EASI reduction after vitamin D supplementation is concordant with the meta-analysis conducted by Fu et al., but as the dose and time of supplementation differed between studies and there were several confounding factors, studies do not allow concluding about the true effect of supplementation on AD[31].

On the contrary other studies have not confirmed the beneficial effect of vitamin D supplementation. A randomized controlled trial concluded that disease severity did not significantly decrease after vitamin D supplementation at a dose of 2000 IU/day for 3 months ($p = 0.7$), despite a significant correlation between lower vitamin D values and disease severity ($p = 0.015$)[45].

Another randomized controlled study evaluating allergic diseases in children after cholecalciferol supplementation in doses of 10 μg (400 IU) or 30 μg (1200 IU), from 2 weeks of life up to 24 months, showed that, although at 12 months 25(OH)D concentrations were significantly higher in the group supplemented with 30 μg of cholecalciferol, there was no statistically significant difference in the development of allergic diseases between the 2 groups[46].

Conclusion

A possible relationship between AD and vitamin D has been a subject of interest by the scientific community, as a deficiency in vitamin D seems to occur frequently in the population, and vitamin D has a role in the regulation of epidermal differentiation and the immune response. Therefore, there is a rational to study the influence of vitamin D in the course of AD and try to understand how vitamin D may influence several factors involved in its pathogenesis, specifically in the dysfunction of the skin barrier, immune dysregulation, and antibacterial defence[26].

Despite scarce and not very robust, many studies have shown a statistically significant association between low serum vitamin D levels and AD, especially in children, with correlation with disease severity, but this does not necessarily suggest a cause-effect relationship between the two variables. UVB phototherapy, recommended for AD treatment, may at least in part act through the increase of vitamin D levels. Nevertheless, although many studies have shown that oral vitamin D supplementation can improve vitamin D status, enhance the expression of AMPs in the skin of AD patients[26], and improve AD severity scores, the results are not always concordant on the capacity to reduce the risk of developing AD or reduce its severity, and topical vitamin analogs have not been approved for the treatment of AD.

Moreover, although several studies have pointed out that vitamin D supplementation may have a potential role in improving the severity and symptomatology of AD, there is no consensus on the dose, treatment duration, or the best time for supplementation. Studies with larger samples with more control on possible confounding factors, and involving more the adult population, are needed to confirm these data[30]. Furthermore, despite incongruent results, some studies suggest a positive influence of higher prenatal values of maternal vitamin D on the onset of AD during childhood and the benefit of vitamin D supplementation during pregnancy or breastfeeding in the prevention of AD in childhood.

With the present data, it is possible to conclude that there is a probable benefit of vitamin D supplementation in improving the symptoms and clinical signs of AD and that this might be an adjuvant treatment for AD. For this, studies with the same methodology, with larger samples and longer duration are needed to obtain more concrete conclusions.

As discussed in a Cochrane analysis (2012) (Dietary supplements for established atopic eczema. Cochrane Database Syst Rev. 2012 Feb 15;2012(2):CD005205) which continues to be very actual, the available studies about vitamin D supplementation in AD are small, with low numbers of participants to even exclude moderate treatment effects, besides the poor quality in terms of the way these studies were run. It is possible that some supplements may have, or may not, an impact on the severity of AD but until we have an appropriate-powered trial with a publicly, transparent registered protocol we are left with poor quality data and a number of meta-analysis and narrative reviews that have to explore that same poor quality data.

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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 no patient data appears 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 appears 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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REVIEW ARTICLE

Dermatological manifestations in endocrine disorders

Manifestações dermatológicas de distúrbios endócrinos

Cael Ostrovski-Sauberlich and Carlos A. Negrato*

Curso de Medicina, Universidade de São Paulo, Bauru, São Paulo, Brazil

Abstract

This article reviews the dermatological manifestations that frequently arise in endocrine disorders, encompassing conditions such as diabetes mellitus, acromegaly, polycystic ovary syndrome, hypothyroidism, Addison's disease, among others. It explores the interactions between the endocrine system and the skin, highlighting how hormonal imbalances can result in a variety of skin symptoms. With a comprehensive approach, it offers important clinical insights for dermatologists and endocrinologists, aiming at a better understanding and an accurate diagnosis of these conditions.

Keywords: Skin manifestations. Endocrine system diseases. Dermatology.

Resumo

Este artigo revisa as manifestações dermatológicas que frequentemente surgem em distúrbios endócrinos, abrangendo condições como diabetes mellitus, acromegalia, síndrome dos ovários policísticos, hipotireoidismo, doença de Addison, entre outras. Explora as interações entre o sistema endócrino e a pele, destacando como desequilíbrios hormonais podem resultar em uma variedade de sintomas cutâneos. Com uma abordagem abrangente, oferece insights clínicos importantes para dermatologistas e endocrinologistas, visando uma melhor compreensão e diagnóstico preciso dessas condições.

Palavras-chave: Manifestações dermatológicas. Doenças do sistema endócrino. Dermatologia.

Introduction

The skin, the largest organ in the human body[1], performs mechanical, immunological, and antimicrobial protection functions and participates in thermal regulation and sensory perception. It also has a rich network of hormone receptors and is therefore sensitive to hormonal changes, which can result in a wide variety of skin manifestations that represent a diagnostic challenge for general practitioners, endocrinologists, and dermatologists[2].

Endocrine disorders can lead to significant changes in the skin and phanera and may serve as clinical markers of these underlying conditions. Cutaneous changes associated with these disorders can range from very mild to very severe, vary from non-specific to specific to the underlying disease, and may appear early or late in the course of these diseases[3].

By understanding the complex interrelationships between the skin and the endocrine system, in several situations, health-care professionals can identify underlying

***Correspondence:**
Cael Ostrovski-Sauberlich
E-mail: caelsauberlich@gmail.com

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endocrine disorders early and provide appropriate and effective treatment, which can significantly improve the quality of life and life-span of these patients[4]. This is particularly important in situations where these cutaneous alterations represent paraneoplastic manifestations of aberrant hormonal production by tumor cells[5].

Acromegaly

Acromegaly is a rare and chronic disease that results from the overproduction of growth hormone (GH) after the closure of the bone epiphyses[6]. It is mainly caused by pituitary adenomas, which produce excess GH and is characterized by an increase in blood levels of GH and insulin-like growth factor type 1 (IGF-1)[7].

The characteristic signs and symptoms of acromegaly are related to increased levels of GH and IGF-1, which results in the overgrowth of soft tissues and organs, with subsequent clinical manifestations, such as enlargement of the extremities (hands and feet), tongue, jaw, facial changes (protruding forehead and enlarged nose), joint pain, sleep disturbances, voice changes, among others.

Dermatological manifestations

The excess GH can cause an increase in skin thickness, which is due to the increase of dermal collagen, and not to the expansion of the epidermis due to the proliferation and maturation of keratinocytes[8]. In addition, these patients may have swollen skin due to the accumulation of glycosaminoglycans in the dermis, which is more prominent on the face, hands, and feet[9]. Skin tags, which are usually related to insulin resistance and diabetes mellitus (DM), are present in most individuals affected by acromegaly. It is unclear if its appearance is due to excess GH and IGF-1 or if it is a consequence of another metabolic dysregulation[10]. Excessive sweating is found in 50% to 88% of patients, due to the trophic effect of GH on the cutaneous sweat glands, as well as growth of the periglandular nerves[11].

Hypothyroidism

Hypothyroidism with low amounts of thyroid hormones results in a lower metabolic rate[12]. The most common causes are Hashimoto's thyroiditis, treatment of hyperthyroidism, surgical removal of the thyroid, or the use of certain medications, such as methimazole, propylthiouracil, and amiodarone[13]. If not properly treated, it can lead to weight gain, fatigue, constipation, depression, infertility, heart disease, and decreased cognitive function. Treatment is done with thyroid hormone replacement[14].

Dermatological manifestations

Dry, cold, and rough skin, due to decreased blood flow and secretion from the acinar glands, in response to a drop in thyroid hormones, are the most common manifestations, resulting in flaking, itching, and hypersensitive skin[14]. Changes in skin pigmentation are also observed. Pallor may occur due to decreased cutaneous blood supply, a yellowish coloration is usually due to increased serum carotene levels, and also cutaneous hyperpigmentation can be observed when hypothyroidism is associated with primary adrenal insufficiency[15].

There may also be weakening of the nails, which become brittle, fragile and prone to flaking. This is due to hypothermia caused by hypothyroidism, resulting from a decrease in metabolic rate, which leads to a compensatory secondary vasoconstriction. Vasoconstriction decreases blood flow, with a deficit in the supply of nutrients and oxygen to skin structures, causing slow growth and brittle nails[16].

The hair may also become coarse, brittle, dry, develop slow growth, and eventually lead to alopecia[17].

In addition, myxedema may occur in the lower limbs, a soft and painless edema, giving the skin a thick and flaccid appearance, especially on the face, periorbital region, hands, and feet which results from the infiltration of the skin with glycosaminoglycans with associated water retention[18].

Hyperthyroidism

The most common causes of hyperthyroidism are Graves' disease[19], and hyperfunctioning thyroid nodules[20]. It can lead to a number of complications, including unintentional weight loss, tachycardia, palpitations, anxiety, tremors, muscle weakness, irritability, insomnia, heat intolerance, exophthalmos, cardiovascular, bone, and fertility changes[21].

Dermatological manifestations

Among the most common dermatological manifestations are warm, moist, and smooth skin. Heat is due to increased cutaneous blood flow and peripheral vasodilation, resulting from increased metabolism and may be accompanied by hyperhidrosis[22]. The skin may appear thin, soft, and fragile, becoming more susceptible to

injuries and bruises, because of the decrease in the keratin layer. Diffuse or generalized alopecia (Fig. 1) may also be found[23].

Nails can present with onycholysis, also called Plummer's nails, which comprises the separation of the nail from the nail bed, and onychodystrophy, which involves changes in the shape and texture of the nails. Some patients may develop cutaneous hyperpigmentation, especially in the areas exposed to the sun. The mechanism is related to cortisol deficiency, due to its accelerated degradation that occurs in these patients, which leads to an increased production of pro-opiomelanocortin (POMC), a prohormone that is subsequently cleaved into adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH). Elevated serum levels of MSH stimulate increased melanin synthesis, which leads to hyperpigmentation[24].

If the cause of hyperthyroidism is Graves' disease, periorbital edema and protrusion of the ocular globe may also be found. This is due to the enlargement of the eye muscles, caused by inflammation due to the accumulation of inflammatory cells and proliferation of fibroblasts in the interstitial tissue. Thus, this muscle enlargement ends up impairing the venous drainage of the orbital contents, causing periorbital and conjunctival edema[25].

Other autoimmune diseases affecting the skin can also observed more frequently in these patients, namely, vitiligo and chronic urticaria[26].

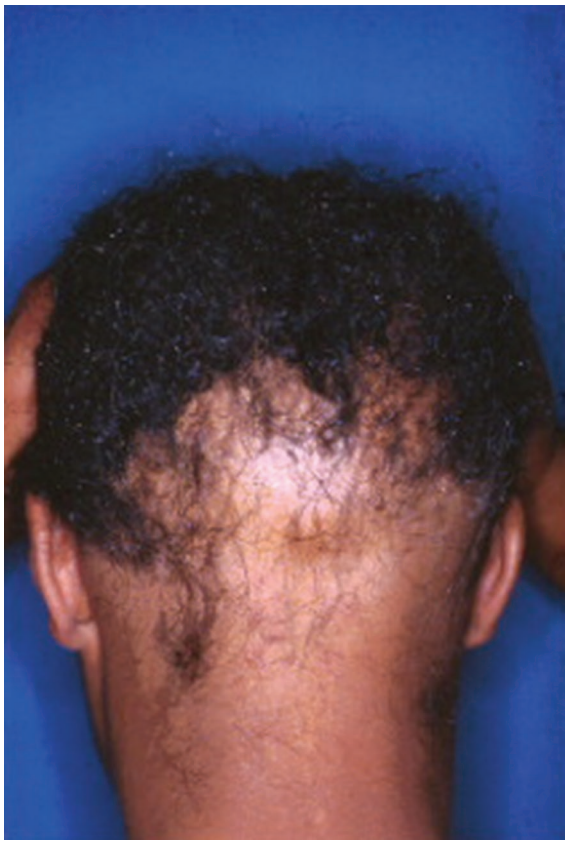

Figure 1. Alopecia in a patient with hyperthyroidism *(source: Lauro de Souza Lima Institute).*

Polycystic ovary syndrome (PCOS)

It affects women of reproductive age and is characterized by hormonal changes that generally lead to the formation of multiple cysts in the ovaries, hyperandrogenism, weight gain, and fertility disorders[27]. Although not yet fully understood, the causes of polycystic ovary syndrome PCOS are associated with genetic and hormonal factors, associated with insulin resistance[28]. Complications such as menstrual irregularities, infertility, obesity, type 2 DM, cardiovascular disease, and mood disorders can occur. Diagnosis is based on clinical criteria, laboratory tests, and imaging[29].

Dermatological manifestations

Several alterations can be found in affected patients, such as hirsutism[29] and acne, resulting from hyperandrogenism[30,31]. This is due to the fact that androgens are the main hormonal regulators of hair growth and sebum production and secretion. In women with PCOS, excess androgen production by the ovaries increases serum levels of testosterone and dihydrotestosterone which interact with androgen receptors in hair follicles and promote differentiation from fleece hair (small, thin, and poorly pigmented) into terminal hair (thick, long, and pigmented)[32] and enhance the activity of sebaceous glands. Hirsutism occurs mainly in the genital area and can progress along the medium line, groins, lumbar region, face, chin, intermammary region, and around the nipples[33]. Acne in PCOS affects especially the face, but also the neck, upper trunk, and back regions.

Acanthosis *nigricans* (Fig. 2), characterized by dark, thick patches of skin, can also be found, especially in areas of body folds, such as the neck, armpits, and groin. It is strongly related to insulin resistance present in PCOS, with excessive production of insulin and IGF-1, which leads to increased stimulation of keratinocytes and fibroblasts[29].

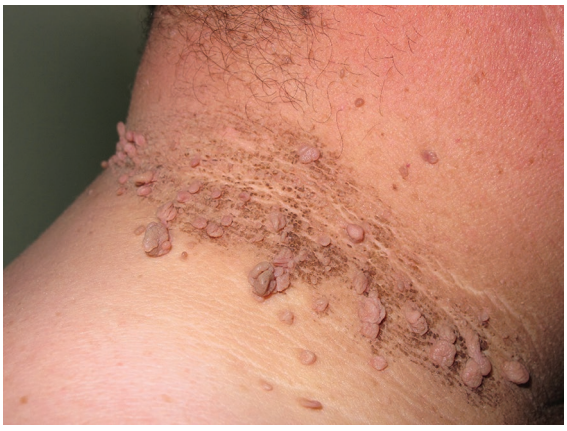

Figure 2. Acanthosis nigricans in a patient with polycystic ovary syndrome *(source: University Hospital of Coimbra).*

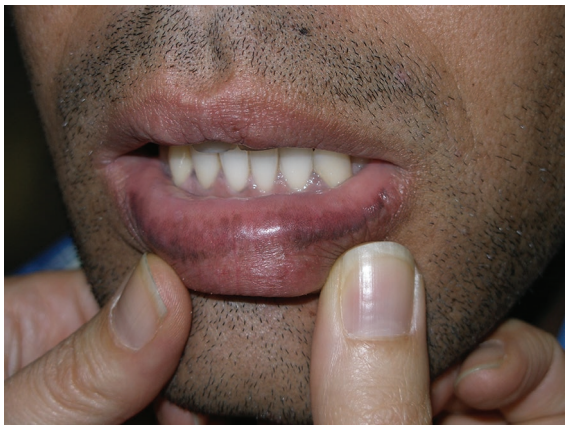

Figure 3. Hyperpigmentation on the lips of a patient with Addison's disease *(source: University Hospital of Coimbra).*

Addison's disease

Addison's disease, also known as primary adrenal insufficiency, is a rare condition[34] resulting mainly from autoimmune destruction of these glands or infections, such as tuberculosis[35]. Addison's disease can lead to serious complications such as fluid and electrolyte imbalance, hypotension, chronic fatigue, weight loss, dizziness, and, in extreme cases, adrenal crisis or Addisonian crisis, a potentially life-threatening medical emergency[36]. Treatment involves replacing deficient adrenal hormones such as cortisol and aldosterone[37].

Dermatological manifestations

Cutaneous hyperpigmentation (Fig. 3) is the most characteristic finding, occurring in about 90% of patients[35], which is a consequence of cortisol deficiency and increased production of POMC and MSH by the hypophysis. Elevated MSH results in increased melanin synthesis in basal melanocytes (Fig. 4), causing hyperpigmentation[36]. This hyperpigmentation is most common in sun-exposed areas and in skin folds, such as joints and scars. The color varies from light brown to dark brown and can be more intense on mucous membranes, such as gums, tongue, cheeks, and lips[38].

Vitiligo, in unequal areas and often bilateral, may be present in 10% to 20% of patients with Addison's disease with autoimmune etiology, due to the autoimmune aggression of melanocytes[39].

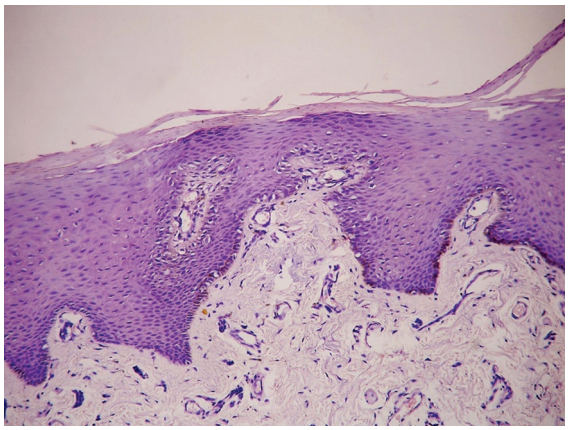

Figure 4. Histopathology (H and E ×40) of basal melanocytes of a patient with Addison's disease *(source: University Hospital of Coimbra).*

Cushing's syndrome

It is a condition that results from excessive exposure to high levels of cortisol[40], which plays an important role in regulating metabolism, the immune system, and stress[41]. The causes of Cushing's syndrome can be varied, including the use of exogenous corticosteroids, tumors in the adrenal glands or pituitary gland, and, in rare cases, cortisol-producing tumors in other organs[42].

The complications of this syndrome can be serious and compromise several systems of the body. In addition to weight gain, patients may have redistribution of body fat, with accumulation in the abdomen and face,

with a decrease in fat tissue in arms and legs[40]. Other signs and symptoms may include muscle weakness, increased blood pressure, emotional changes, menstrual irregularities in women, and sexual dysfunction in men. In addition, these patients may have osteoporosis and DM[41].

Dermatological manifestations

One of the most prevalent manifestations is the presence of stretch marks in various regions of the body, such as the abdomen, thighs, arms, and breasts[42] (Fig. 5), which are reddish or purplish in the acute phase and become thinner and whitish over time[43]. Their presence is related to the reduction in skin elasticity caused by excess cortisol, which decreases the production of collagen and elastin, important components for skin integrity. High levels of cortisol can also inhibit cell regeneration and proper skin healing. When the skin is thin, it is more vulnerable to injury, and may present frequent bruising[44].

Another common skin manifestation when the cause is a pituitary tumor producing high levels of ACTH is hyperpigmentation, which can develop in sun-exposed areas, as well as in skin folds, armpits, groin, and neck. The skin in these areas may become darker, and the coloration may vary from light brown to dark brown[45].

Cushing's syndrome can also lead to the development of oily skin and monomorphic papular acne, due to the hyperstimulation of the sebaceous glands caused by cortisol. Facial erythema and flushing can also be found, especially on the cheeks and nose, a condition known as facial erythema[46].

Hypopituitarism

Hypopituitarism is a rare condition that can occur due to damage or dysfunction in the pituitary gland itself or in the surrounding structures, due to the presence of pituitary tumors, traumatic injuries, infections, inflammations, and complications after cranial surgeries or radiation therapy or post-partum (Sheehan syndrome)[47].

The clinical manifestations of this disease can be diverse, such as excessive fatigue, unintentional weight loss, muscle weakness, menstrual disorders in women, sexual dysfunction in men, changes in growth and development in children, hypotension, stress intolerance, and metabolic disorders, among others[48].

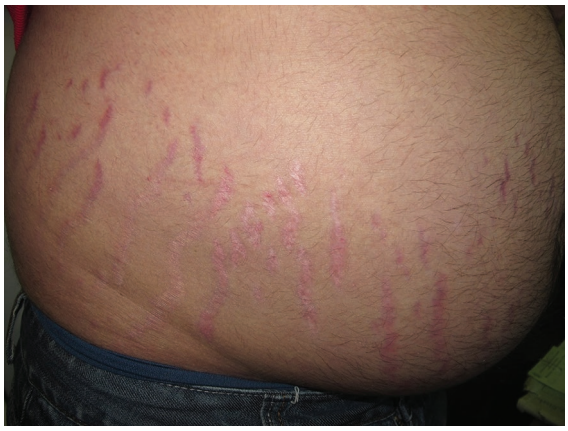

Figure 5. Stretch marks in a patient with Cushing's syndrome *(source: University Hospital of Coimbra).*

Dermatological manifestations

Dermatologic findings depend on which glands are compromised and which hormones are insufficient. In case of insufficiency in the production of thyroid-stimulating hormone the skin may become dry, cold, and rough, due to the resulting hypothyroidism, with all the clinical manifestations of this disease[4].

In addition, the decrease in the production of gonadotropins follicle-stimulating hormone, and luteinizing hormone results in secondary hypogonadism in men and women, with a consequent decrease in body hair and also alopecia, since sex hormones are essential for the maintenance of hair and hair follicles[44].

DM

DM is characterized by altered insulin secretion and varying degrees of peripheral insulin resistance, causing hyperglycemia and abnormal glycosylation of several molecules, namely, hemoglobin (HbA1C) whose levels are accurately related to the glycemic control[49]. Initial symptoms are related to hyperglycemia and include polydipsia, polyphagia, polyuria, and blurred vision. Late complications include vascular disease, peripheral neuropathy, kidney disease, and predisposition to infections[50]. Most complications can be postponed or prevented with adequate glycemic control[51].

There are two main types of DM: type 1 and type 2 DM.

Type 1 DM is an autoimmune disease in which the immune system attacks and destroys insulin-producing pancreatic beta cells, leading to absolute insulin

deficiency[49]. Type 2 DM, on the other hand, is characterized by insulin resistance and/or deficiency[50]. While type 1 DM usually develops at younger ages and cannot be prevented, type 2 DM generally occurs in people older than 45 years and is strongly associated with obesity, physical inactivity, and family history, and can often be prevented or delayed with lifestyle changes[49].

Dermatological manifestations

Diabetic dermopathy is present in about 40% of patients and is often related to some DM-related chronic complication, such as kidney disease, retinopathy, or neuropathy[52]. The disease tends to appear in the lower extremities and in older men and can result from minor trauma[53]. It is characterized by painless, and rarely itching, atrophic and hyperpigmented macules, located on the anterior region of the legs. They are oval or round, depressed, shiny, irregularly contoured, sometimes bilateral but with asymmetrical distribution[54].

Skin infections occur in 20-50% of patients with DM[55], particularly in those with type 2 DM. Overall, they are associated with poor glycemic control. Several factors favor the onset of infections in these patients, mainly those with chronic vascular or neurological complications. Alterations in immune response are frequently found, especially reduced neutrophil chemotaxis and phagocytosis, with increased adhesion between epithelial cells and pathogens (such as *Candida albicans* in the oral and vaginal mucosa and *Escherichia coli* in the urinary tract)[56].

Acanthosis nigricans often precedes the diagnosis of hyperglycemia, is characterized by dark, thick patches of skin, and is most often found in areas of body folds, such as the neck, armpits, and groin. It is strongly related to insulin resistance, which promotes the excessive production of IGF-1, which leads to hyperstimulation of keratinocytes and fibroblasts. The result is the appearance of hyperkeratosis and epidermal papillomatosis, which can be observed in histopathological analysis. Hyperkeratosis is mainly responsible for the clinical manifestation[28].

Vulvovaginal candidiasis is a prevalent disorder found in women with DM (Fig. 6), especially in those with poor glycemic control, and is a frequent cause of vulvar pruritus[56]. It is clinically manifested by erythema of the genital area (with or without fissures) and satellite pustules. It is sometimes accompanied by whitish vaginal discharge. Its pathophysiology is related to the immune deficit of individuals with DM since they present inhibition of neutrophil activity, which increases the proliferation, adhesion, and virulence of this microorganism[57].

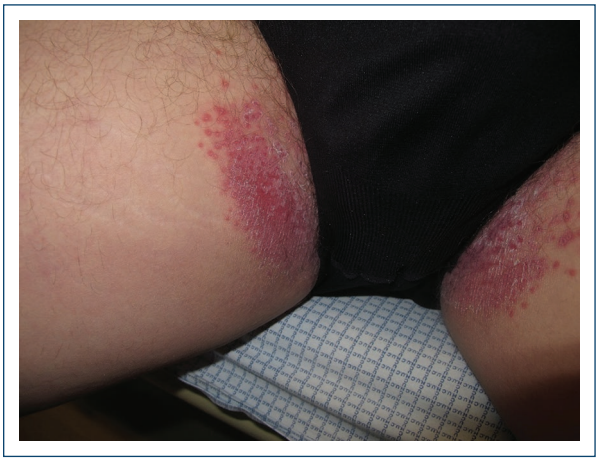

Figure 6. Groin candidiasis in a type 1 diabetic patient with poor glycemic control *(source: University Hospital of Coimbra).*

Diabetic foot is the most devastating of DM-related complication. It is usually due to a combination of vasculopathy, neuropathy, and mechanical trauma, which occurs in 15-25% of all people with DM, and in about a quarter of these patients can lead to the onset of infections and osteomyelitis, which can lead to amputation of the affected limb[58]. It is generally due to an unnoticed trauma to cutaneous areas with neuropathy and calluses, such as on the soles of the feet and tips of toes. The healing process is generally seriously compromised, due to hyperglycemia, impaired chemotaxis, cell proliferation, and migration[59]. In addition, the increase in pro-inflammatory chemokines hinders wound healing, leading to the appearance of plantar ulcers. The presence of neuropathy and vasculopathy in these feet can cause muscle atrophy and bone deformation, with important changes in bone architecture, causing the collapse of the arch of the foot, a condition called Charcot foot.

Chronic pruritus is a common manifestation of DM, occurring in 3-49% of patients, significantly affecting their quality of life[60]. Diabetic polyneuropathy with sweating dysfunction due to sympathetic nervous system impairment may play a role in the pathogenesis of pruritus in these patients[61].

Vitiligo (Fig. 7), is found in 2-10% of patients with type 1 DM[62], occurring spontaneously with a progressive course. Its pathophysiology is related to autoimmune mechanisms, an intrinsic characteristic of this type of DM[63].

Necrobiosis lipoidica (Fig. 8) affects 0.3-1.2% of all patients with DM, with a higher prevalence in women than

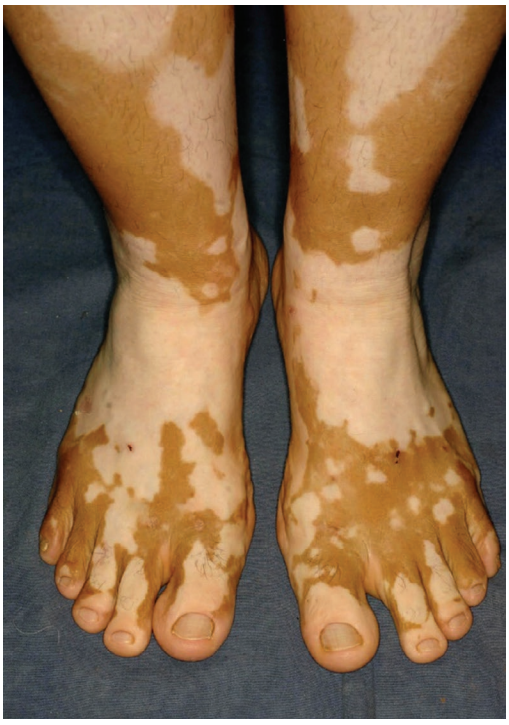

Figure 7. Vitiligo in a patient with type 1 diabetes *(source: Lauro de Souza Lima Institute).*

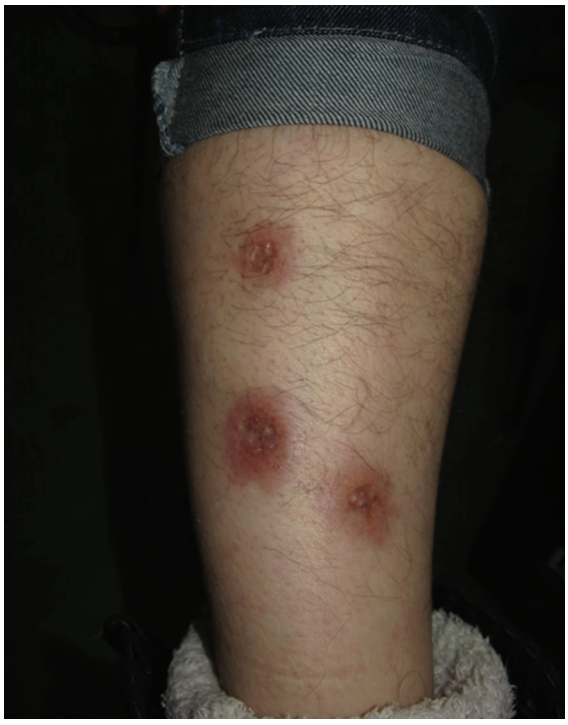

Figure 8. Necrobiosis lipoidica in a patient with type 2 diabetes *(source: University Hospital of Coimbra).*

in men, and is commonly located in the ventral area of the legs, often with symmetrical distribution[64]. It usually begins with erythematous papules, which slowly evolve into a brownish-yellow plaque with atrophic center and telangiectasia. In up to 35% of patients, lesions may ulcerate and present secondary bacterial infections. The pathophysiological mechanisms are still unknown, but the histopathology of the lesions shows degeneration of dermal collagen with a palisading granulomatous inflammatory infiltrate under an atrophic epidermis[65]. Glycemic control has no significant effect on the evolution of these lesions, and no study has convincingly proven the efficacy of the various types of drugs used in the treatment of necrobiosis lipoidica, namely, topical or intralesional corticosteroids injected into the lesion edges, and also ultraviolet A[56].

Conclusion

The cutaneous manifestations associated with endocrine disorders are varied and may serve as valuable clinical markers for these underlying conditions. Understanding the complex interactions between the skin and the endocrine system is crucial for early identification of endocrine disorders and providing appropriate treatment. The examples covered in this narrative review article highlight how dermatological examination can play a key role in the detection and management of endocrine diseases, significantly improving the quantity and quality of life of patients. Therefore, collaboration between dermatologists, endocrinologists, and general practitioners is essential for effective diagnosis and treatment of these complex and often underdiagnosed conditions.

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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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REVIEW ARTICLE

Skin microbiome in diabetes mellitus: a literature review

Microbioma cutâneo na diabetes mellitus: uma revisão da literatura

Sofia R. Rodrigues[1,2], Carla Mottola[1,3], and João Borges-da Costa[4,5,6,7]*

[1]USF Damião de Góis, Unidade de Saúde Local Lisboa Ocidental; [2]APDP, Portuguese Diabetes Association; [3]Nova Medical School; [4]Dermatology Department, Hospital de Santa Maria, Unidade de Saúde Local Lisboa Norte; [5]Dermatology University Clinic, Faculdade de Medicina da Universidade de Lisboa; [6]Institute of Hygiene and Tropical Medicine, Universidade Nova de Lisboa; [7]Institute of Preventive Medicine and Public Health, Faculdade de Medicina da Universidade de Lisboa. Lisbon, Portugal

Abstract

The authors performed a review to investigate if there are alterations in the skin microbiome among individuals with diabetes mellitus (DM) and to assess how these alterations may contribute to specific skin conditions and complications associated with this disease. On December 1st, 2023, searches on the PubMed® and ScienceDirect databases were conducted, using the Mesh Terms "skin microbiome" AND "DM", limiting the results to those published in the last 10 years. The authors identified seven articles, including two reviews and five original research papers. Both type of papers revealed that individuals with DM exhibited significant less diversity in terms of microbial richness, with a notable colonization by *Staphylococcus* spp. In conclusion, the skin microbiome appears to be impaired in individuals with DM. However, more longitudinal studies are necessary to determine whether this impairment is a consequence of DM and to understand how it may interfere with DM complications.

Keywords: Diabetes mellitus. Skin microbiome. *Staphylococcus aureus.*

Resumo

Os autores pretendem esclarecer se existem alterações no microbioma cutâneo em pessoas com Diabetes Mellitus (DM), passíveis de predispor a patologia cutânea e complicações desta doença. As bases de dados PubMed® e ScienceDirect foram pesquisadas a 1 de dezembro de 2023, utilizando os Mesh Terms "skin microbiome" AND "diabetes mellitus", limitando os resultados aos artigos publicados nos últimos 10 anos. Obtiveram-se 7 artigos, incluindo 2 revisões e 5 artigos de investigação original. Ambos os tipos de artigos revelaram que a pele das pessoas com DM apresenta uma diversidade microbiana significativamente menor, com uma forte colonização de *Staphylococcus* spp. Em conclusão, o microbioma da pele parece estar alterado nos indivíduos com DM Contudo, são necessários mais estudos longitudinais para compreender se esse comprometimento é consequência da DM e como pode interferir nas complicações da doença.

Palavras-chave: Diabetes mellitus. Microbioma da pele. *Staphylococcus aureus.*

***Correspondence:**
Sofia R. Rodrigues
E-mail: sofiafrr@hotmail.com

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Introduction

The skin microbiome refers to a diverse community of microorganisms, including bacteria, fungi, and viruses, that reside on the skin's surface. Most of these microbes are recognized as commensal, playing a vital role in maintaining the overall health and functioning of the skin, although sporadically they may cause skin infections[1].

Bacteria are the most abundant type of microorganisms found on the skin, while fungi are the least abundant. This predominance persists even in cutaneous regions, such as the feet, characterized by a high level of fungal diversity. According to the topography and skin conditions, a unique microenvironment can be created into the skin, which can be categorized into three distinct regions: the sebaceous, moist, and dry areas[1].

The gut microbiota profile in type 2 diabetes mellitus is similar to that observed in other inflammatory pathologies with subclinical inflammation[2]. It is expected that in T2D, the skin microbiome has different characteristics from normoglycemic individuals. This holds particular relevance due to the complications of T2D, especially in the foot, where an impaired microbiome may lead to higher prevalence of infections[3].

In this review, we intend to clarify if alterations occur in the skin microbiome among individuals with diabetes mellitus (DM) and how these alterations may contribute to specific skin conditions and complications associated with the disease.

Methods

A systematic review, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was performed using PubMed® and Web of ScienceTM databases on December 1st, 2023, using the Mesh Terms "skin microbiome" AND " DM" limited to papers written in English and published in the past 10 years. The papers obtained from these searches were combined and duplicates were removed.

All the abstracts from each field were reviewed by two different authors.

The papers retrieved, including reviews and research articles, were considered, while case reports were excluded from the study.

Results

As represented in figure 1, we obtained 50 papers to analyze (22 from PubMed and 28 from ScienceDirect). One duplicate was eliminated, and 20 papers were excluded due to the absence of "skin microbiome" or "diabetes" in the abstract. In addition, one paper was excluded because it was written in German.

After excluding these 22 papers, the authors reviewed the remaining 28 papers. Of these, three did not align with the objective of this review, and three described animal studies.

The remaining papers consisted of two reviews[4,5] and five primary studies or research articles[6-10], all of which were thoroughly analyzed.

The review led to the conclusion that patients with DM have a higher proportion of *Staphylococcus aureus* in the skin microbiome than healthy controls[4,5]. Poor glycemic control was associated with a greater colonization of *Staphylococcus* spp. and *Streptococcus* spp[5].

One review singled out the top ten bacterial, eukaryotic, and viral species commonly found in various anatomical regions, including dry, moist, sebaceous, and foot skin.

Dry skin in non-diabetic individuals tends to be colonized more frequently by *Cutibacterium acnes*, *Corynebacterium tuberculostearicum*, and *Streptococcus mitis*. Among eukaryotic species, *Malassezia restricta*, *Malassezia globosa*, and *Aspergillus tubingensis* are the most commonly encountered. Moist skin harbors a higher proportion of *C. tuberculostearicum*, *Staphylococcus hominis*, *C. acnes*, as well as fungi like *M. globosa*, *M. restricta*, and *Tilletia walkeri*.

Sebaceous skin is enriched with *C. acnes*, *Staphylococcus epidermidis*, and *C. tuberculostearicum*, along with fungi such as *M. restricta*, *M. globosa*, and *Malassezia sympodialis*.

Notably, *S. aureus* does not appear among the ten most prevalent bacterial species in any anatomical region representative of dry, moist, or sebaceous skin.

Several primary studies included the analysis of foot samples collected from various sites, including the plantar surface of the foot (both from wound and intact skin, either dry or moist)[6], intact skin from the plantar arch of the feet (dry skin)[8], the fourth interdigital area of the feet (moist skin)[9], chronic skin lesions of the lower limbs (moist and dry skin)[7], and both the plantar forefoot (dry skin) and the interdigital space (moist skin)[10]. However, many of these studies lacked comprehensive descriptions of the features and findings across these different foot areas, hindering proper comparisons. In addition, these studies exclusively focused on patients with type 2 diabetes among individuals with diabetes[6-10].

Concerning diabetic foot ulcers (DFUs), the superficial ones, namely, those of short duration, were associated with a predominance of *Staphylococcus* spp., particularly *S. aureus*. In contrast, deeper ulcers and those of longer duration exhibited greater microbial diversity, with a higher relative abundance of anaerobic

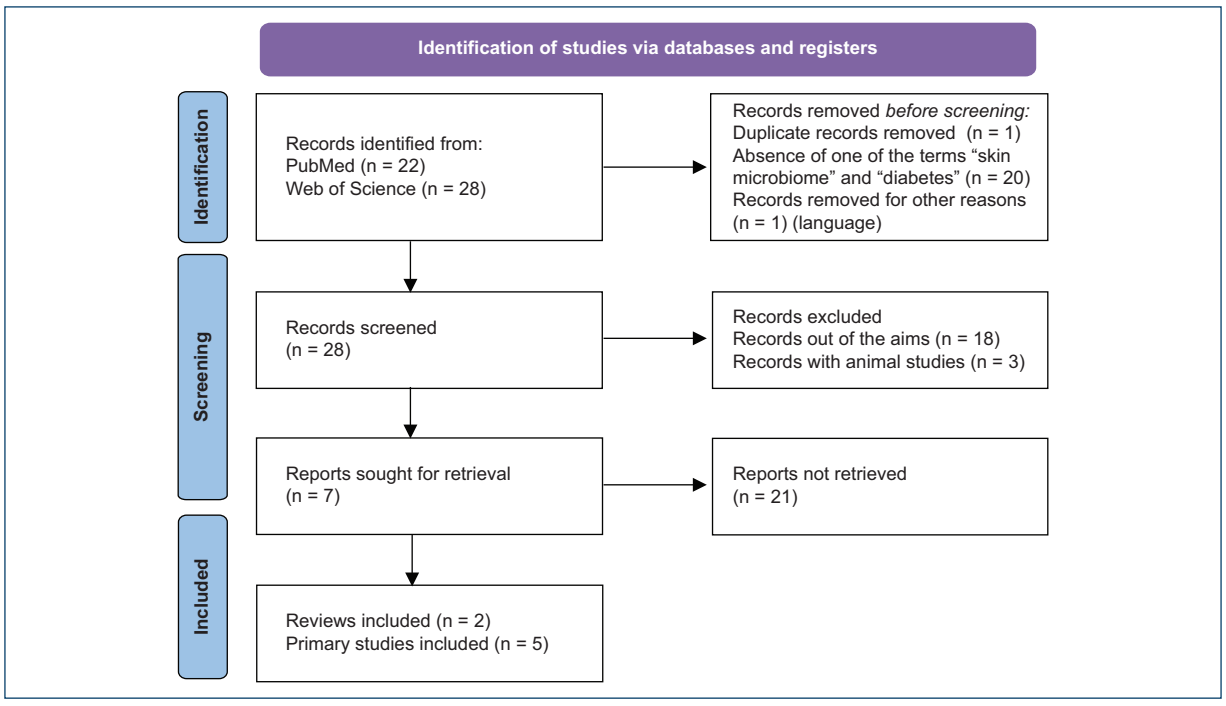

Figure 1. Flow diagram of the literature review using MESH terms "skin microbiome" and "diabetes mellitus".

bacteria and Gram-negative *Proteobacteria* spp. However, the specific period of evolution of these ulcers was not clarified[5]. *Cladosporium herbarum* and *Candida albicans* were identified as the most abundant fungal species found on DFUs. The presence of increased fungal diversity, along with the formation of polymicrobial biofilms consisting of fungi and bacteria, was associated with poor clinical outcomes in chronic wounds[5].

Primary cross sectional studies included 8-41 participants in each group (individuals with DM and controls), and studies performed cultural examination, 16S ribosomal RNA sequencing or PCR of the fungal internal transcribed spacer (ITS2) region. These studies revealed that the skin microbiome in individis uals with diabetes, both for bacteria and fungi, was significantly less diverse than in control subjects[6-8]. Chronic wounds tended to be dominated by the most abundant skin *Staphylococcus*[6,9]. A significant association between T2D status and heavy colonization by *S. epidermidis* (OR-5.40, p = 0.02) was found[9].

The bacteriological colony test revealed a higher proportion of both positive bacteriological colony tests and respective polymicrobial result among the individuals with T2D[10]. This phenomenon confirms an alteration in the skin microbiome of diabetic subjects, indicating a modification in the "opportunistic role" of some species of the skin bacterial flora[10].

The 16S rRNA gene sequencing demonstrated dynamic changes in the skin microbiome of the foot during the progression of DM. In patients with DM, the dominant skin microbial phyla were *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Bacteroidetes*[7,8].

A single study conducted in China[8] investigated the variations in the microbiome among individuals with type 2 DM, without associated complications, across different durations of the disease.

In summary, individuals classified into short-term DM (< 2 years), middle-term DM (5-8 years), and long-term DM (more than 10 years) categories exhibited notable alterations in the microbial community structures of their foot skin compared to the control group (without DM). Moreover, these changes were found to be positively correlated with the duration of the illness[8].

At the onset of the disease (short-term DM group), there was a slight reduction in the abundance of Proteobacteria, which steadily increased as the disease progressed (long-term DM group). Conversely, the abundance evolution of actinobacteria displayed an opposite pattern. In addition, the diversity of low-abundance microbes increased with disease progression. All three DM groups demonstrated higher microbial diversity compared to the control group, with the long-term diabetes group exhibiting the highest diversity among the short- and middle-term groups[8]. Regarding fungi, *Trichophyton rubrum* was more abundant in DM samples in, exhibiting a lower Shannon diversity index for fungi[8].

Discussion

Reviews have underscored the direct involvement of microorganisms in regulating the skin's immune response.

It is speculated that *S. aureus* colonization in individuals with DM predisposes them to minor-to-moderate foot infections and even life-threatening bloodstream *S. aureus* infections, throughout the skin inflammation and an immune response. The role of *S. aureus* juxtaposes to that in a model of atopic dermatitis, in which *S. aureus* cutaneous colonization could elicit skin inflammation and induce an immune response[4]. The proposed mechanisms involves the activation of an inflammatory cascade, intensified by the exposure to *S. aureus* on the skin surface, which promotes IL-36a production by keratinocytes (partly through the activity of PSMa), which triggers IL-36R/MyD88 signaling on T cells to produce IL-17A/F. In addition, it is suggested that colonization with *S. aureus* could impair the suppressive activity of Treg cells and staphylococci have the ability to produce lipoprotein acids that can inhibit skin inflammation through a TLR-dependent pathway. The inhibition of complement component C5a receptors reduces the diversity of the skin microbiota, while symbiotic flora can regulate the expression of certain complement genes in the skin, thereby modulating immunity[4].

A shared observation across these primary studies is the loss of microbiologic diversity in DM and the increased risk of developing skin infections associated with microbiome dysbiosis.

It was suggested that microbiome dybiosis in T2D could stem from the same activated innate immune response thought to be central to the development of T2D. The extent to which alterations in the microbiome at one organ site influence distal organs or different organ sites remains unclear. In addition, it is uncertain whether these systemic effects are specific to particular tissues or organs, along with the underlying mechanisms involved[9].

For the reasons mentioned so far, targeted microbiome modulation reveals such a promising candidate that was recently discovered to exert anti-inflammatory and beneficial metabolic functions, that can mitigate dysbiosis and combat pathogens[4,5].

The majority of the previously cited studies adopted a cross-sectional design, incorporating a relatively small number of patients. Yet, more longitudinal studies are needed to understand if this impairment is a cause or a consequence of DM and to elucidate how it might interfere with DM complications.

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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 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

Dupilumab in pediatric atopic dermatitis: real-world evidence from two national centers

Experiência com dupilumab na dermatite atópica em idade pediátrica: dados do mundo real de dois centros nacionais

*Gilberto P. da Rosa[1,2], Patrícia Amoedo[1], Pedro Matos[1], Ana Pedrosa[1,2], Ana Nogueira[1], Catarina Vilarinho[3], Fernando Mota[3], Maria J. Cruz[1,2], Filomena Azevedo[1], and Alberto Mota[1,2,4]**

[1]Department of Dermatology and Venereology, Centro Hospitalar Universitário de São João, Porto; [2]Department of Medicine, Faculty of Medicine, University of Porto, Porto; [3]Department of Dermatology and Venereology, Hospital da Senhora da Oliveira, Guimarães; [4]CINTESIS@RISE, Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto. Portugal

Abstract

Objective: The use of dupilumab in children with atopic dermatitis (AD) demonstrated clinical efficacy in clinical trials. Nevertheless, real-world evidence is still limited. We aim to provide data on this matter regarding a Portuguese pediatric population. **Methods:** Retrospective analysis of patients with AD below the age of 18 treated with dupilumab in two Portuguese hospitals. Data regarding previous therapies, activity scores, and adverse reactions were collected. **Results:** Thirty patients were included in the analysis (19 male patients, 63%), with a median age of 14 years (2-17 years). The median follow-up after starting treatment was 80 weeks. The median baseline Eczema Area and Severity Index (EASI) score was 32.3. Sixty percent of patients achieved EASI-90 and 77% EASI-75 at week 16 (n = 30); 79% EASI-90 and 92% EASI-75 at week 52 (n = 24); 64% EASI-90 and 82% EASI-75 at week 104 (n = 11); and 75% EASI-90 and 100% EASI-75 at week 132 (n = 4). Regarding adverse reactions, four patients (12%) presented facial erythema and two patients had eosinophilia above 2000/μL and conjunctivitis. In five patients (17%), there was a need for a dose increase, with treatment failure occurring in two patients (7%). **Conclusion:** Our data corroborated the evidence from clinical trials, highlighting the maintained efficacy and adequate safety profile of dupilumab in this age group.

Keywords: Atopic dermatitis. Dupilumab. Monoclonal antibody. Pediatrics. Real world.

Resumo

Objetivo: O uso de dupilumab em crianças com dermatite atópica (DA) demonstrou eficácia clínica em ensaios clínicos. No entanto, a evidência do mundo real é ainda limitada. Este trabalho pretende fornecer dados relativos a este domínio, numa população pediátrica portuguesa. **Métodos:** Análise retrospetiva de doentes com DA com idade inferior a 18 anos, tratados com dupilumab, em dois hospitais portugueses. Foram recolhidos dados sobre terapêuticas prévias, *scores* de atividade e reações adversas. **Resultados:** Trinta doentes foram incluídos na análise (19 doentes do sexo masculino, 63%), com uma mediana de idades de 14 anos (2-17 anos). O seguimento mediano após o início do tratamento foi de 80 semanas.

***Correspondence:**
Alberto Mota
E-mail: ajvmota@med.up.pt

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O *score* EASI basal mediano foi de 32,3. Sessenta por cento dos doentes alcançaram EASI-90 e 77% EASI-75 na semana 16 (n = 30); 79% EASI-90 e 92% EASI-75 na semana 52 (n = 24); 64% EASI-90 e 82% EASI-75 na semana 104 (n = 11); 75% EASI-90 e 100% EASI-75 na semana 132 (n = 4). Em relação a reações adversas, 4 doentes (12%) apresentaram eritema facial e 2 doentes eosinofilia superior a 2000/μL e conjuntivite. Em 5 doentes (17%), houve necessidade de aumento de dose, com falência do tratamento em 2 doentes (7%). **Conclusão:** O tratamento com Dupilumab na DA em idade pediátrica num ambiente de mundo real corroborou os dados dos ensaios clínicos, destacando a eficácia mantida e o perfil de segurança adequado neste grupo etário.

Palavras-chave: Dermatite atópica. Dupilumab. Anticorpo monoclonal. Pediatria. Mundo real.

Introduction

The introduction of dupilumab, a monoclonal IgG4 antibody that inhibits the action of both interleukin (IL)-4 and IL-13, constituted a revolutionary milestone in the management of atopic dermatitis (AD). In adulthood, approval in Europe and the United States occurred in 2017, with its efficacy initially demonstrated in three phase III trials: LIBERTY AD SOLO1 and SOLO2[1,2], versus placebo, and LIBERTY AD CHRONOS[3], with the addition of topical corticosteroids in both dupilumab and placebo groups. In addition, an extension of the SOLO 1 and II trials (LIBERTY AD SOLO-CONTINUE)[4] revealed a maintained clinical efficacy of up to 36 weeks, but there are data already supporting the persistence of this effect up to 76 weeks[5], 3 years (LIBERTY AD OLE)[6], and 4 years[7].

Regarding the pediatric population, there has also been consistent progress in the use of the drug. Evidence from the LIBERTY AD ADOL (12-17 years)[8] and LIBERTY AD PEDS (6-11 years)[9] trials allowed for extrapolation of efficacy and safety data from the adult population to this age group, culminating in FDA and EMA approval for the use of dupilumab from 12 years of age in 2019 and from 6 years of age in 2020. More recently, favorable data from the LIBERTY AD PRESCHOOL[10] trial served as the basis for FDA approval in 2022 and EMA approval in March 2023 for the use of the drug from 6 months of age. In adolescents, data on the extension of dupilumab use up to 52 weeks are additionally available, with the achievement of Eczema Area and Severity Index (EASI)-75 in 81% of the recruited individuals[11].

At present, we witness the emergence of so-called real-world evidence regarding the efficacy of dupilumab in patients with AD. While in the adult population, there is already significant evidence devoted to this matter[12], in the pediatric population, the number of publications is still limited. A prospective multicenter Italian study including 139 adolescents with AD displayed a mean EASI reduction of 79.8% at week 16[13], a result superior to that observed in clinical trials. A Chinese publication, including 15 children with AD, observed a significant reduction of the mean EASI score from 19.2 to 1.69 at up to 6 months of follow-up[14]. A study from the United States featuring 23 children and adolescents with AD who received dupilumab for 1 year or more revealed an achievement of EASI-75 in all patients and EASI-90 in 60.8% of them[15]. Finally, a Dutch publication involving 61 children and adolescents with AD, described, at 28 weeks of therapy, 75.4%, 49.2%, and 24.6% of patients reaching EASI-50, EASI-75, and EASI-90, respectively[16].

Although these data already hint at a favorable performance of dupilumab in pediatric populations in a real-world setting, there is a visible need for additional evidence, namely in what pertains to longer periods of follow-up. We aim to provide real-world data on this matter in a Portuguese pediatric population.

Methods

Retrospective analysis of clinical charts of patients with AD below the age of 18 treated with dupilumab under follow-up in two Portuguese tertiary hospitals. Data regarding comorbidities, previous therapies, activity scores (EASI, NRS-pruritus, and DLQI), and adverse reactions were collected.

Statistical analysis was performed using IBM SPSS Statistics 28. Categorical variables are reported as proportions and/or percentages. Continuous variables are reported as mean (± SD) or median (range) values, depending on normal distribution. The correlation between categorical variables was obtained by performing a Chi-square test.

Results

Thirty patients were included in the analysis (19 male patients, 63%), with a median age of 14 years (IQR 8.5-16 years, min-max 2-17 years). Information on patient's allergic comorbidities is available in table 1.

Table 1. Patients' previous therapies, allergic comorbidities, and observed adverse reactions

Previous therapies	
≤ 1 immunosuppressant	6 (20)
≥ 2 immunosuppressants	24 (80)
Oral corticosteroids	28 (93)
Cyclosporine	23 (77)
Methotrexate	5 (17)
Azathioprine	5 (17)
Mycophenolate mofetil	4 (13)
Omalizumab	1 (3)
Atopic comorbidities	
Allergic rhinitis	15 (50)
Asthma	14 (47)
Conjunctivitis	1 (3)
Adverse reactions	
Facial erythema	4 (13)
Eosinophilia (> 2000/μL)	2 (7)
Conjunctivitis	2 (7)
Herpes virus infections	1 (3)
Injection-site reaction	0 (0)
Skin infections	0 (0)

The previously most used immunosuppressants were oral corticosteroids (28 patients, 93%), cyclosporine (23 patients, 77%), methotrexate, and azathioprine (both in five patients, 17%). The median follow-up after starting treatment with dupilumab was 80 weeks (IQR 52-104 weeks). Median baseline EASI score was 32.3 (IQR 25.7-40). Sixty percent of patients achieved EASI-90 and 77% EASI-75 at week 16 (n = 30); 62% EASI-90 and 79% EASI-75 at week 28 (n = 29); 79% EASI-90 and 92% EASI-75 at week 52 (n = 24); 78% EASI-90 and 78% EASI-75 at week 72 (n = 18); 64% EASI-90 and 82% EASI-75 at week 104 (n = 11); and 75% EASI-90 and 100% EASI-75 at week 132 (n = 4). In five patients (17%), there was a need for a dose increase, with treatment failure occurring in two patients (7%) – one primary and one secondary failure. In two patients (7%), there was a worsening of the EASI score during therapy with dupilumab after an initial favorable response, with a subsequent reattainment of disease control while maintaining therapy. Ninety-seven percent of patients (n = 29) achieved an EASI score below 7, 97% (n = 29) EASI-50, and 93% (n = 28) EASI-75 and EASI-90 at some point of follow-up. Complete results are shown in table 2. Ninety-three percent of patients (n = 28) achieved at some point a reduction superior to 4 points in the NRS pruritus scale and of more than 6 points in the DLQI questionnaire. Regarding the most common adverse reactions, four patients (12%) presented facial erythema, two (7%) patients asymptomatic eosinophilia above 2000/μL, and two (7%) patients mild conjunctivitis (Table 1). All events were manageable or transient and there was no need to stop treatment.

Discussion

Our results suggest that treatment outcomes with dupilumab in pediatric AD in a real-world setting corroborate those observed in clinical trials, even surpassing them in some cases.

Our data reports 77% of patients achieving EASI-75 at week 16, a value higher than those observed in pediatric trials: in the LIBERTY AD ADOL (12-17 years)[8] trial, achieved by 42% of patients in the every-2-week regimen and 38% in the every-4-week regimen; in the LIBERTY AD PEDS (6-11 years)[9] trial, achieved by 67% of patients in the every-2-week regimen and 70% in the every-4-week regimen; and in the LIBERTY AD PRESCHOOL[9] trial (6 months-5 years), achieved by 53% of patients. Comparing our data with other real-world evidence studies, the value EASI-75 at week 16 observed in 77% of our patients also surpasses the available evidence, with reported values ranging from 43 to 65%[13,15,16]. Regarding long-term outcomes, our results fall in line with the reported literature, with the LIBERTY AD PED-OLE[11] trial in adolescents providing evidence on the extension of dupilumab use up to 52 weeks, with EASI-75 in 81% of recruited individuals, whereas a real-world study from the United States featuring 23 children and adolescents with AD who received dupilumab for 1 year or more revealed an achievement of EASI-75 in all patients[15]. In our case, 93% of patients achieved EASI-75 and EASI-90 at some point of follow-up, being noteworthy that our cohort displays a median follow-up of 80 weeks, with patients followed up to 132 weeks. Our cohort also provides relevant data in what concerns the significant reduction of the NRS pruritus score and DLQI in the vast majority of our patients, highlighting the impact of treatment, not only in disease activity scores but also on the quality of life reported by patients, as already stressed by other real-world publications[16]. An additional novel information added by our data regards the specific treatment outcomes of need for dose increase and treatment failure, with the former occurring in 17% and the latter in 7%. In addition, the fact that, in two patients, there was a worsening of the EASI score during therapy with dupilumab after an initial favorable response, with subsequent reattainment of disease control with maintained therapy, strengthens the rationale of not suspending the treatment at the first signs of clinical deterioration.

Table 2. Eczema Area and Severity Index (EASI) score at different follow-up points

	Timepoint					
Disease activity	**Week 16 (n = 30)**	**Week 28 (n = 29)**	**Week 52 (n = 24)**	**Week 72 (n = 18)**	**Week 104 (n = 11)**	**Week 132 (n = 4)**
Median EASI	3 (1-8.2)	2 (1-6)	1 (0-3)	1.5 (0-3.8)	2 (0-6.1)	4.5 (0-8.9)
EASI 75	23 (77)	23 (79)	22 (92)	14 (78)	9 (82)	4 (100)
EASI 90	18 (60)	18 (62)	19 (79)	14 (78)	7 (64)	3 (75)

Regarding safety and adverse reactions, pediatric clinical trials revealed no serious events, with conjunctivitis and injection-site reactions as the most common occurrences[8,9], whereas, in real-world pediatric studies, conjunctivitis, flushing, joint pain, and headache featured among the most reported[13,14-16]. In our cohort, conjunctivitis was also present, but facial erythema and asymptomatic eosinophilia were additionally noted. No serious events occurred, corroborating the previously observed safety of dupilumab.

Our study presents both strengths and limitations. On the one hand, our sample is composed of a significant number of pediatric patients, originating from two different centers, featuring detailed data on their evolution across a substantial time span. On the other hand, data were collected retrospectively, with expectable shortcomings, and two-thirds of the patients were above the age of 11, a fact that might constitute the source of certain biases, making our data particularly applicable to this age group.

Overall, treatment with dupilumab in pediatric AD in a real-world setting corroborated the data from clinical trials, highlighting its maintained efficacy and adequate safety profile in this age group.

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None.

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 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

Novel combination of NB-UVB phototherapy with bFGF-related decapeptide 0.1% and CO_2 laser in the treatment of stable, non-segmental vitiligo

Nova combinação de fototerapia NB-UVB com decapeptídeo relacionado a bFGF 0,1% e laser de CO_2 fracionado no tratamento de vitiligo estável não segmentar

Navleen Kaur, Jasleen Kaur, and Saurabh Sharma*

Department of Dermatology, Venereology and Leprosy, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India

Abstract

Objective: This study aimed to assess the efficacy of a combination therapy involving NB-UVB phototherapy, bFGF-related decapeptide, and fractional CO2 laser in stable non-segmental vitiligo cases. **Method:** A prospective interventional study was conducted on clinically stable, non-segmental vitiligo patients. The combination therapy was administered for 16 weeks, and patients were followed up for 12 weeks. Data analysis was performed using SPSS version 23.0, with statistical significance set at $p < 0.05$. **Results:** Twenty patients aged 12-60 years were enrolled. After 16 weeks, 65% of patients showed good to excellent repigmentation (> 50%) with perifollicular repigmentation being commonly observed. The time for initial repigmentation was as early as 4 weeks. Adverse effects were mild and transient, with no recurrence observed during the follow-up period. **Conclusion:** This novel combination therapy demonstrated significant repigmentation rates in stable non-segmental vitiligo and presents a potential safe and efficacious therapeutic option in clinical settings.

Keywords: Narrow-band ultraviolet B. Basic fibroblast growth factor-related decapeptide. Fractional CO_2 laser. Stable vitiligo. Non-segmental vitiligo.

Resumo

Objetivo: Este estudo teve como objetivo avaliar a eficácia de uma terapia combinada envolvendo fototerapia NB-UVB, decapeptídeo relacionado a bFGF e laser de CO2 fracionado em casos estáveis de vitiligo não segmentar. **Métodos:** Um estudo intervencionista prospectivo foi conduzido em pacientes com vitiligo não segmentar, clinicamente estáveis. A terapia combinada foi administrada por 16 semanas e os pacientes foram acompanhados por 12 semanas. A análise dos dados foi realizada no SPSS versão 23.0, com significância estatística definida como valor $p < 0.05$. **Resultados:** Vinte pacientes com idades entre 12 e 60 anos foram incluídos. Após 16 semanas, 65% dos pacientes apresentaram repigmentação boa a excelente (> 50%), sendo comumente observada repigmentação perifolicular. O tempo para repigmentação inicial foi de 4 semanas. Os efeitos adversos foram leves e transitórios, sem recorrência observada durante o período de acompanhamento. **Conclusão:** Esta nova terapia combinada demonstrou taxas de repigmentação significativas no vitiligo não segmentar estável e apresenta uma opção terapêutica potencialmente segura e eficaz em ambientes clínicos.

Palavras-chave: NB-UVB. Decapeptídeo relacionado a bFGF. Laser de CO2 fracionado. Vitiligo estável. Vitiligo não segmentar.

***Correspondence:**
Navleen Kaur
E-mail: navleenk85@gmail.com

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Introduction

Vitiligo is an acquired disorder of pigmentation of the skin characterized by depigmented macules and patches as a result of the loss of melanocytes in the epidermis. The disease can affect any age, gender, or ethnicity but has a significant psychosocial impact, especially in those with higher skin phototype[1]. The distinctive feature of vitiligo is widespread cutaneous and mucosal depigmentation, which is linked to genetics, autoimmunity, oxidative stress, melanocyte self-destruction, and the release of cytokines[2]. Vitiligo is categorized into two primary forms based on clinical criteria, namely, segmental vitiligo, and non-segmental vitiligo, with the latter encompassing various subtypes such as generalized vitiligo, acrofacial vitiligo, and universal vitiligo[3]. The stability of vitiligo holds crucial importance for treatment approaches and prognosis, thus garnering significant attention in research and clinical practice[4]. Although the ideal length of time for the disease to be considered stable clinically is still debatable, the general consensus recommends a time period of the past 1 year of a patient having no new lesions, no progression of the existing lesions, and absence of Koebnerization for labeling a case as stable vitiligo[5]. Koebner's phenomenon is an important aspect in determining whether surgical or invasive treatments are suitable for vitiligo cases, making the stability of the disease a critical aspect in its management.

Although numerous topical and systemic modalities of treatment are available, there is still a search for the ideal therapeutic modality since the response to treatment is not much satisfactory[6].

Narrow-band ultraviolet B (NB-UVB) therapy, implemented since 1997, has emerged as one of the most effective and safest therapies for the treatment[7,8]. The light source used for NB-UVB phototherapy has a peak emission at 311 nm and is very effective in vitiligo since it can stimulate the dormant skin melanocytes and also modulate the cutaneous immune system[9].

Fractional carbon dioxide laser (CO_2) functions through fractional thermolysis, and it is suggested to enhance vitiligo treatment by reducing the affected area by causing shrinkage of the tissue, encouraging melanoblast migration from surrounding healthy skin, and promoting post-inflammatory pigmentation[10-12].

Even though the precise etiology of the disease is yet unknown, it is well established that the pathophysiology of the disease is significantly influenced by the absence of basic fibroblast growth factor (bFGF) as the patients have been proven to have reduced bFGF mRNA expression in the lesions[13]. Thus, melanocyte growth and migration are facilitated by bFGF through a variety of signaling mechanisms and hence finds the role of bFGF-related decapeptide 0.1% in the treatment of vitiligo.

The melanocyte growth factor deprivation theory serves as the foundation for the decapeptide therapy of vitiligo, and the clinical data from Indian clinical studies substantiates the use of decapeptide as a medication for vitiligo management[14].

The present study investigated the effect of a novel combination therapy involving NB-UVB phototherapy, bFGF-related decapeptide 0.1%, and fractional CO_2 laser in the management of stable cases of non-segmental vitiligo and aims to provide novel insights into the treatment of the disease.

Materials and methods

The study was conducted after taking approval from the institutional ethical committee. All patients of clinically stable, non-segmental vitiligo attending Dermatology outpatient department of a tertiary care hospital from March 2023 to May 2023 were recruited in this prospective, interventional study after taking informed consent (from guardians in case of minors). Study subjects were selected based on the inclusion and exclusion criteria. A brief history along with details of any previous treatment taken was documented and confidentiality of the patients was ensured.

Inclusion criteria

The following criteria were included in the study:

- Patients in the age group of 12-60 years.
- Patients with lesions stable for at least 1 year, having non-segmental vitiligo.
- Patients who are not on any treatment for the past 3 months.

Exclusion criteria

The following criteria were excluded from the study:

- Patients with active Koebner's phenomenon.
- Patients with mucosal vitiligo.
- Patients with active inflammation, infection, or ulcer in or around the vitiligo lesion.
- Females who are pregnant or are planning pregnancy; lactating mothers.

– Immunosuppressed patients, patients with chronic inflammatory diseases, systemic lupus erythematosus, xeroderma pigmentosa, and history of skin cancer.

Data analysis

The data were analyzed using Statistical Package for the Social Sciences version 23.0 software (SPSS Inc., Chicago, IL, USA for Windows), and valid conclusions were drawn by using the Chi-square test. $P < 0.05$ was considered statistically significant.

Procedure

Photographs were taken for the record before starting the procedure, at every session, and then during follow-up. Patients were exposed to NB-UVB chamber starting from 200 mJ/cm^2 regardless of the skin phenotype, and an increment of 10-20% dose per session was done till a minimal erythema dose was achieved (pink, asymptomatic erythema lasting < 24 h). Two such sessions were done per week. Along with this, patients were asked to apply 1 mg/mL of bFGF-related decapeptide once every day, 2 h before bedtime. The lesions were exposed to fractional carbon dioxide laser at every 4 weekly interval @ 50 mJ energy and 100-200 spots/cm^2 spot density according to the size of the lesion, after achieving anesthesia with topical anesthetic cream containing 2.5% prilocaine and 2.5% lidocaine. The laser was done before the NB-UVB exposure and an area of around 2 mm beyond the lesion was exposed. Four such sessions of fractional CO_2 laser were carried out. Duration of therapy was 16 weeks and assessment of the patient was done at every 4-week interval using a quartile grading scale.

Follow-up

Patients were followed up every 4 weeks for 12 weeks after the last session. Any adverse effects experienced by the patients were documented during this follow-up period.

Results

A total of 22 patients met the inclusion-exclusion criteria during the stipulated time period and were enrolled in the study; however, two patients were lost to follow-up and hence were excluded from the study. Among these 20 patients, 8 (40%) were males and 12 (60%) were females (Fig. 1). The most common age group seen was 29-45 years (60%) and most patients belonged to skin types 3 and 4 (80%). Two female patients had a positive family history of vitiligo (10%) and two had hypothyroidism (10%). Disease duration was longer than 5 years for most patients (55%) and 85% of the patients had previous treatments (not within the past 3 months of study enrolment) (Table 1). The most common sites of lesions were the abdomen and lower back (15% each), followed by other sites as shown in figure 2.

The time taken for initiation of repigmentation was as early as 4 weeks after beginning the therapy, as observed in six patients (30%). The median time to the beginning of repigmentation was found to be 8 weeks. The most common type of repigmentation was perifollicular (Fig. 3A and B), followed by diffuse and marginal, with 65% of patients (13 out of 20) showing statistically significant repigmentation ($p = 0.03$), considered as good (51-75%, i.e., grade 3) or excellent (> 75%, i.e., grade 4) repigmentation (Table 2) (Fig. 4A and B). Lesser response (grade 1-2), that is, < 50% repigmentation was seen at acral and relatively less hairy sites.

All patients experienced mild pain, redness, swelling, and slight burning sensation after the laser procedure but symptoms subsided after ice application or within a few hours after the treatment and were tolerable. Two patients also complained of a slight burning sensation after the 0.1% bFGF-related decapeptide application, but this was described as tolerable and subsided within a few minutes after the application. Similarly, one patient experienced mild itching, xerosis, and slight erythema post-NB-UVB exposure but the complaints were transient and resolved after application of an emollient.

Hyperpigmentation and therefore, change in skin type was observed in 11 (55%) patients (Fig. 4B). None of the patients reported any local infection, koebnerization, or increase in size of lesions. No adverse effects such as scarring, ulceration, telangiectasias, hypertrophic, or atrophic scars were noted.

No recurrence of lesions was observed at the end of follow-up period of 12 weeks in any of the patients.

Discussion

Vitiligo is a pigmentary skin disorder characterized by the absence of melanocytes in the epidermis, leading to the development of depigmented macules and patches on the body[15]. A variety of treatment options are available for vitiligo, including topical and systemic medications, phototherapy, laser therapy, and surgical

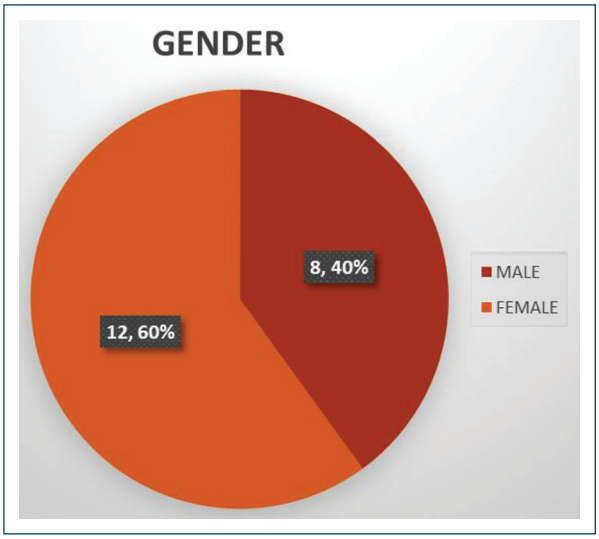

Figure 1. Gender-wise distribution of the patients enrolled in the study; 40% (8 out of 20) of patients enrolled were males, and 60% (12 out of 20) were females.

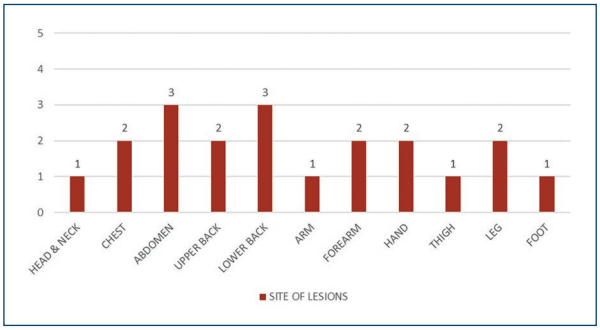

Figure 2. Distribution of patients according to the site of vitiliginous lesions; mucosal vitiligo was not included in the study (numerals indicate the number of patients).

Table 1. Demographic details and brief history of the patients enrolled in the study

Parameter	No. of patients	Percentage of patients
Age (in years)		
12-28	6	30
29-45	12	60
46-60	2	10
Fitzpatrick skin type		
1	0	0
2	1	5
3	6	30
4	10	50
5	3	15
6	0	0
Family history of vitiligo		
Present	2	10
Absent	18	90
History of hypothyroidism		
Present	2	10
Absent	18	90
Duration of disease (in years)		
< 1	0	0
1-5	9	45
> 5	11	55
History of previous treatment (not within past 3 months of enrollment)		
Present	17	85
Absent	3	15

interventions. While the topical treatments typically involve the use of corticosteroids, calcineurin inhibitors, bFGF-related decapeptide, vitamin D analogs, and ruxolitinib, there is the minimal response with topical therapy alone, thereby warranting the addition of systemic or combination therapy. Surgical therapy, on the other hand, is limited to segmental or localized stable vitiligo that is not involving a large body surface area[16]. Phototherapy is a commonly employed treatment modality and is effective for inducing repigmentation not only in early disease but also in disease of prolonged duration[17]. NB-UVB phototherapy, administered 2-3 times weekly with a wavelength of 311 nm, is widely utilized, as it helps in repigmentation by stimulating melanocyte activity, thus having more efficacy and relatively low risk of side effects compared to psoralen photochemotherapy which was previously used for management of vitiligo[17,18]. The addition of topical bFGF-related decapeptide could potentially enhance this effect, as bFGF is known for its role in promoting cell growth and differentiation by acting as a mitogen, thus, aiding melanocyte regeneration[19]. Shah et al. in their study have demonstrated that bFGF-related peptide (bFGFrP) exhibits synergistic effects when combined with other treatment modalities for vitiligo[20]. Similarly, fractionated CO_2 acts by skin resurfacing, tissue shrinkage, activation, and migration of melanoblasts from the hair follicles and melanocytes from the skin surrounding the vitiliginous lesions[21]. Furthermore, it is known to stimulate Matrix metalloproteinase-2, thereby promoting migration of melanocytes from the adjacent skin as caused by NB-UVB and causes better penetration of topical drugs by creating micropores[22,23]. The efficacy of fractional CO_2 laser therapy in treating refractory non-segmental vitiligo was demonstrated in

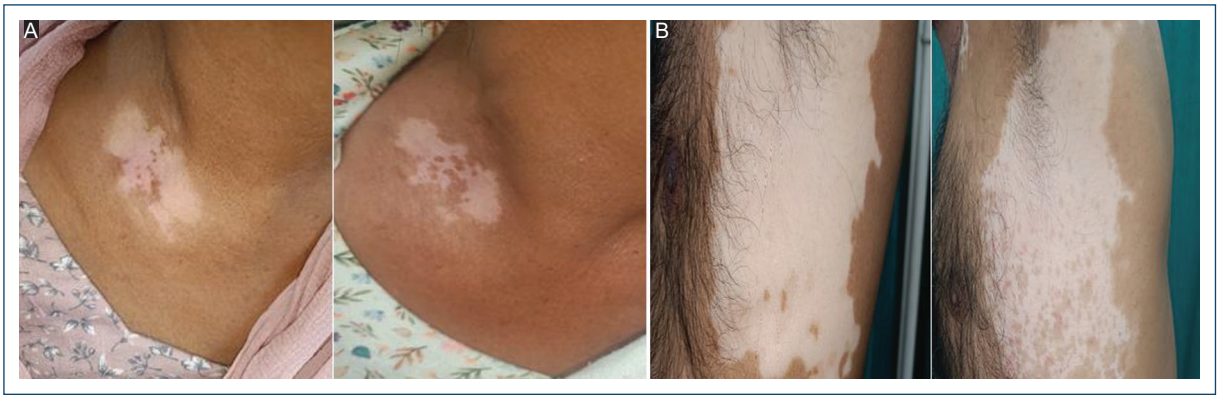

Figure 3. A: perifollicular type of repigmentation seen in a 43-year-old female patient at 4 weeks after the initiation of treatment (site of lesion- right side of neck). **B:** perifollicular type of repigmentation seen in a 41-year-old male patient at 4 weeks after the initiation of treatment (site of lesion - left side of chest).

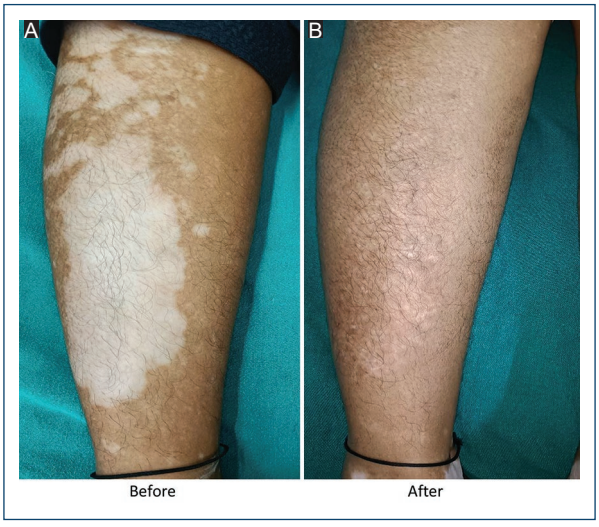

Figure 4. A: grade 4 (> 75%) repigmentation observed in a 36-year-old female patient at the end of 16 weeks of study (site of lesion- right leg). **B:** grade 4 (> 75%) repigmentation observed in a 42-year-old female patient at the end of 16 weeks of study; hyperpigmentation was noted in the surrounding skin (site of lesion - lower back).

a study conducted in 2014 where traditional treatments had been ineffective[12]. Therefore, fractional CO_2 laser acts by facilitating penetration of the bFGFrP and improving melanocyte uptake, while also promoting skin remodeling.

In the present study, a novel combination of NB-UVB phototherapy with bFGF-related decapeptide 0.1% and fractional CO_2 laser was used in patients of non-segmental, stable vitiligo which demonstrated early initiation of repigmentation (within 4 weeks) and the pattern of repigmentation most commonly observed was perifollicular. Moreover, the results obtained in the study were statistically significant ($p = 0.03$), which confirmed the efficacy of the combination in the management of vitiligo. The results obtained were similar to the study done in 2012 by Shin et al.[24], which proved higher efficacy of the combination of fractional CO_2 with NB-UVB as compared to NB-UVB alone. However, contrary to the results of > 50% repigmentation obtained in 10% of patients only, our study showed similar results in 65% of patients with the novel combination used. Similarly, Vachiramon et al.[25], in 2016, found better results of the triple combination of fractional CO_2 laser with NB-UVB phototherapy and 0.05% clobetasol propionate cream as compared to dual combination of NB-UVB and 0.05% clobetasol propionate cream, proving the efficacy of fractional CO_2 laser in the treatment of vitiligo. Contrarily, the results obtained with the triple combination used in their study yielded > 50% repigmentation in 23.1% of patients only. Another study conducted in 2023 by Nayak et al.[26] showed a better grade of repigmentation in vitiliginous patches when PUVA phototherapy was combined with bFGFrP as compared to PUVA monotherapy alone, thereby proving the synergistic effect of phototherapy with bFGFrP. However, while 61.8% of patients showed > 50% repigmentation with this combination, our study showed the same results in 65% of patients.

Lesions at the acral and glabrous sites, on the other hand, showed lesser response to treatment (< 50% repigmentation). This difference in results could be explained by the lack of stimulation or mobilization of melanoblasts from the outer root sheath of hair follicles surrounding the vitiliginous lesions at these regions,

Table 2. Grades of repigmentation and gender-wise distribution at the end of 16 weeks of study (p = 0.03); percentage of patients showing good (51-75%) to excellent (> 75%) repigmentation as observed in the study - 65% (13 patients); p = 0.03

Grade of repigmentation	Percentage of repigmentation	Male	Female	Total no. of patients (%) (n = 20)	p-value
Grade 4 (excellent response)	> 75%	2	3	5 (25)	0.03
Grade 3 (good response)	51-75%	6	2	8 (40)	
Grade 2 (moderate response)	26-50%	0	5	5 (25)	
Grade 1 (minimal response)	1-25%	0	2	2 (10)	
Grade 0 (no response)	NIL	0	0	0	

since the melanoblast activation and migration are essential processes for repigmentation of the lesions, as observed in previous studies[21].

To the best of our knowledge, this combination used in the current study has not been studied before. This study proves the efficacy of the combination in the treatment of vitiliginous lesions without any major adverse effects and, hence, can be a safe potential future therapy for the management of stable, non-segmental vitiligo patients.

Conclusion

Although there are certain limitations such as the absence of a comparative group, lack of control area for measuring the efficacy of either modality alone, lesser duration of follow-up to monitor for the loss of achieved pigmentation, exclusion of mucosal vitiligo cases, and a relatively small sample size, the present study demonstrates significant results regarding the efficacy of this novel combination therapy. Combining NB-UVB phototherapy with bFGF-related decapeptide 0.1% and fractional CO_2 laser treatment yielded better grades of repigmentation at a faster rate compared to the combinations of other modalities used previously. This approach offers a safe and effective treatment option, warranting further research to validate its efficacy and broader application in clinical practice.

Funding

None.

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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ORIGINAL ARTICLE

Assurance versus frustration: a retrospective single-center analysis of female patients with acute telogen effluvium

Segurança versus frustração: uma análise retrospetiva num único centro de doentes do sexo feminino com deflúvio telogénico agudo

Erkin Pekmezci

Department of Dermatology, Istanbul Medipol University, International Faculty of Medicine, Istanbul, Turkey

Abstract

Objective: Acute telogen effluvium (ATE) is a scalp hair disorder featured by diffuse, non-scarring shedding with higher female predilection. In general, the disorder is perceived as extremely frightening and urges the patient to visit a physician immediately. We retrospectively analyzed the 3-month prognosis of the female patients with hair loss complaint. **Methods:** Two-hundred and sixty-six female patients who were referred to our hospital with ATE were retrospectively recruited. The patients were analyzed for serum iron, iron-binding capacity, vitamin B_{12}, folate, thyroid-stimulating hormone, and prolactin values. All were prescribed standard zinc and vitamin E supplements in addition to needed medications and invited to a second visit after 3 months. **Results:** All of the mean values for all parameters were found in normal ranges. Two hundred and nine patients came to the second visit after the 3-month treatment period. Of these patients, 9.1% stated hair shedding ceased completely, 74.6% diminished to some extent, and 16.3% continued as before. **Conclusions:** Mainly due to normal mean values, none of the analyzed parameters can be accused as the cause of hair sheddings. The frustrations of the patients are so great that it is reasonable to prescribe some supplements, at least for their placebo effects. Treatment for ATE is primarily reassurance and counseling.

Keywords: Acute telogen effluvium. Etiology. Treatment.

Resumo

Objetivo: O deflúvio telogênico agudo (DTA) é uma condição do couro cabeludo caracterizada por uma queda difusa e não cicatricial, com maior incidência no sexo feminino. Geralmente, a doença é percebida como altamente alarmante, levando os pacientes a buscar imediatamente assistência médica. Neste estudo, analisamos retrospectivamente o prognóstico de três meses em mulheres com queixa de queda de cabelo. **Método:** Duzentos e sessenta e seis pacientes do sexo feminino encaminhados ao nosso hospital com DTA foram recrutados retrospectivamente. As pacientes foram submetidas à análise dos níveis séricos de ferro, capacidade de ligação do ferro, vitamina B12, folato, hormônio estimulante da tireoide e prolactina. Todas receberam prescrição de suplementos padrão de zinco e vitamina E, além dos medicamentos necessários, e foram convidadas para uma segunda consulta após três meses. **Resultados:** Todos os valores médios dos parâmetros analisados estavam dentro da faixa normal. Dentre os 209 pacientes que compareceram à segunda consulta após o tratamento de três meses, 9,1% relataram cessação completa da queda de cabelo, 74,6% experimentaram diminuição em alguma medida, e 16,3% mantiveram o quadro como antes.

Correspondence:
Erkin Pekmezci
E-mail: erkinpekmezci@gmail.com

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Conclusões: Principalmente devido aos valores médios normais, nenhum dos parâmetros analisados pode ser atribuído como causa da queda de cabelo. As frustrações dos pacientes são tão significativas que é razoável prescrever alguns suplementos, ao menos pelos efeitos placebo que podem proporcionar. O tratamento do DTA consiste essencialmente em tranquilizar e aconselhar os pacientes.

Palavras-chave: Deflúvio telogénico agudo. Etiologia. Tratamento.

Introduction

Telogen effluvium is a scalp disorder featured by diffuse, non-scarring hair loss[1]. It may be caused by any disturbance to the hair cycle, resulting in increased and synchronized telogen shedding[2]. Acute telogen effluvium (ATE) is defined as hair shedding lasting for < 6 months[1] and more frequent in the third decade of life[3]. Chronic telogen effluvium is a condition lasting for more than 6 months with a prolonged unpredictable course and it usually affects middle-aged women[1]. In general, the cases of ATE are subclinical, and therefore, its true incidence or prevalence is mostly unknown[2]. An excessive hair shedding without the formation of a glabrous area is a common phenomenon[4]. Both males and females are affected, but the ratio of females is higher. Nevertheless, it should be regarded that women consider hair-shedding problems more seriously and they probably seek medical help more often[1]. Despite the subjective complaints of excessive hair loss, objective attributes may completely be absent[2]. However, the disorder is so frightening that it urges the patient to visit a physician immediately[4]. Patients usually complain of increased hair loss during washing or brushing. They may even bring in bags of shed hair to prove the quantity of loss. They are often very anxious that they will go bald if this goes on. On examination, in general, there is a normal scalp with an absence of inflammatory signs or follicular miniaturization[2]. Any evidence of erythema, scaling, inflammation; altered hair density; changes in shaft caliber, length, shape, or fragility may indicate other diagnoses[5].

ATE may be related to various offenses that can be physical, chemical, or emotional. In general, hair loss occurs approximately 3 months after the trigger exposure[1], however, the observation of increased telogen hair shedding does not always suggest a cause. In addition, the patients usually do not relate these events to the recent insults they faced[6], and the cause remains unknown in many cases[1]. The histopathology of the ATE is non-specific and looks like that of a normal scalp. This may be due to a delayed biopsy, generally performed when the harmful event is no longer active because of the notorious 3-month lag[4]. Increased physiological stress such as surgical trauma and hemorrhage, high fever, and chronic systemic illness can cause ATE[1]. Thyroid dysfunction, hyperandrogenism, and hyperprolactinemia are catagen-inducing endocrine disorders[2]. Thyroid receptors exist in outer root sheath cells and they regulate the frequency of the hair cycle. In general, while hypothyroidism results in decreased frequency of anagen, hyperthyroidism leads to thin hairs. The severity of hair loss is not directly related to the severity of the endocrine abnormality and telogen effluvium can be the only manifestation of subclinical hypothyroidism[7]. Androgens show an inhibitory effect on the hair follicles of the scalp[8]. The mechanism of prolactin in regulating hair growth is related to its inhibitory effect on hair shaft elongation and the premature induction of the catagen phase. Prolactin is also recognized as an androgen metabolism modulator, increasing the level of free testosterone and dehydroepiandrosterone sulfate[9]. Childbirth can also cause excessive hair to enter the telogen phase[1]. Micronutrients such as vitamins and minerals play an important, but not entirely clear role in normal hair follicle development. The roles of folate and vitamin B_{12} in nucleic acid production imply that they may have functions in the highly proliferative hair follicle physiology. Furthermore, the association of hair loss and iron deficiency has been debated for many years[10]. Numerous drugs can cause telogen hair loss and even changes in the dosage of drugs can also lead to excessive shedding. Drugs that can cause telogen effluvium include oral contraceptives, androgens, retinoids, beta-blockers, angiotensin-converting enzyme inhibitors, anticonvulsants, and antidepressants[1]. Emotional stress is commonly ascribed as a cause of ATE. Stress is probably a negative hair growth modulator in humans, presumably with profound effects[2]. It is both an inducer of telogen effluvium and a concomitant response secondary to hair loss. Neurohormones, neurotransmitters, and cytokines are secreted during the systemic stress response. The existence of a brain-hair follicle axis is suggested to represent the specific relationship between a stressor and a premature arrest of the hair cycle[11].

In this study, it was retrospectively analyzed the 3-month outcome of the female patients who referred to our hospital with ATE without any visible sign.

Methods

Two hundred and sixty-six caucasian female patients between 13 and 58 years old, who referred to our hospital dermatology outpatient clinic with hair loss complaints, which began in the last 6 months, in the years 2017-2019 (that is, before the COVID-19 pandemic, which is known to cause telogen effluvium frequently) were retrospectively recruited. All of the procedures were performed in rapport with the ethical principles established for medical research (Helsinki Declaration of World Medical Association 1975, and amendments as revised in 1983). The mean age (MA) ± standard deviation (SD) of the patients was 28 ± 10. They declared excessive shedding which was noticed by themselves or other households. The patients were not using any topical or systemic medications at least for 3 months, they had no scalp or hair disease and none of them were pregnant or in the lactation period. On examination of each patient, there was an essentially normal scalp with an absence of inflammatory signs or follicular miniaturization, and hairs had normal thickness. There were no signs or symptoms of hyperandrogenism. The patients did not declare a solid physical or mental stress in 3 months before the initiation of the complaints. All patients were analyzed for the same parameters in the biochemistry blood laboratory. The searched parameters and their lowest and highest normal values were iron: 40-150 μg/dL, iron-binding capacity (IBC): 200-400 μg/dL, vitamin B_{12}: 134-590 pg/mL, folate: 2.4-12.6 ng/mL, thyroid-stimulating hormone (TSH): 0.27-4.2 μU/mL, and prolactin: 3.34-26.72 ng/mL. The patients were analyzed in five different age groups, each corresponding to a decade. The age groups, MA ± SD, and patient numbers in each group are depicted in figure 1.

For treatment, all patients were prescribed 400 IU vitamin E (α-tocopherol) and 50 mg zinc supplements daily, whether they had all normal or some outside normal laboratory values. In addition to standard supplements, the medications prescribed to the patients with abnormal values were; for iron deficient patients 80 mg Fe^{+2}/day PO, for vitamin B_{12} deficient patients 1 mg cyanocobalamin/day PO both for 3 months; and for the patients with hyperpolactinemia 0.250 mg cabergoline once in every 3 days PO, 1 mg total. All the patients were requested to use the prescribed supplements and medications according to the instructions and invited to a second visit 3 months later.

Results

The mean value ± SD of each parameter according to age groups and each mean value's percentile score

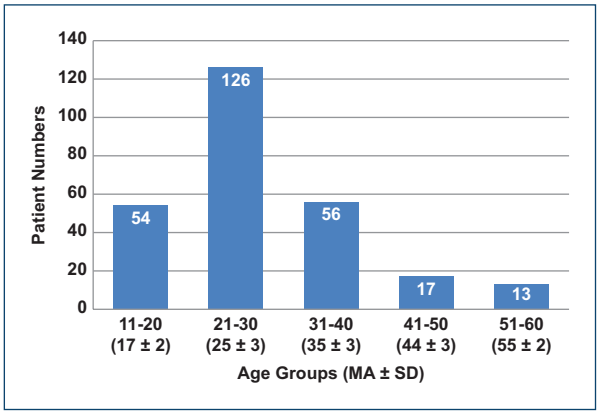

Figure 1. The distribution of patients in each decade and their mean age ± standard deviation values. MA ± SD: mean age ± standard deviation.

(PS) are shown in table 1. All of the mean values for all parameters were in normal ranges in all age groups. PS denotes the place of any normal mean value in the whole normal range of relevant parameters and is calculated as: Current Mean Value-Lowest Limit of Normal Range (LLNR)/Highest Limit of Normal Range (HLNR)-LLNR. In general, it should be emphasized that, although in normal ranges, iron PSs in all age groups were closer to the lowest limit, when compared with the PSs of other parameters.

The patients whose values were outside the normal ranges were also analyzed (Table 2). Without regarding the age groups, all of the patients with abnormal values were included in this analysis, grouping them as; those who have mean values lower than the LLNR, mean values higher than the HLNR, and sum of the first two items as outside the limits of normal range (OLNR). Furthermore, the ratios of mean values to LLNR and HLNR for all parameters were calculated to assess the divergences of abnormal values from the normal ranges. As it is seen in table 2, the highest divergence of low values is –27% (that is, iron: 0.73-1/1) and of high values is +43% (that is, TSH: 1.43-1/1) from LLNR and HLNR, respectively. It should also be stated that in addition to relatively low divergence ratios, the ratios of patients having abnormal values in the whole patient population for any single parameter are also quite low (that is, OLNR%, between 4.5% and 6.4%). It is mentionable that the patients who had iron values lower than LLNR and the patients who had IBC values higher than HLNR were the same individuals. Folate levels were quite consistent and neither low nor high levels were found in all patient population. All patients who

Table 1. The mean value ± standard deviation of each parameter according to age groups and each mean value's percentile score

Age group	Iron	IBC	Vitamin B_{12}	Folate	TSH	Prolactin
11-20						
MV ± SD	82 ± 22	292 ± 54	341 ± 135	7.9 ± 1.6	2 ± 0.8	16 ± 7
PS	38.1	46	45.3	53.9	44	54.1
21-30						
MV ± SD	79 ± 24	302 ± 55	328 ± 114	7.7 ± 1.4	1.9 ± 1	17 ± 10
PS	35.4	51	42.5	51.9	41.4	58.4
31-40						
MV ± SD	72 ± 22	316 ± 68	336 ± 134	7.6 ± 1.6	2.2 ± 1.8	12 ± 5
PS	29	58	44.2	50.9	49.1	37
41-50						
MV ± SD	71 ± 24	313 ± 44	334 ± 140	8.2 ± 1	1.7 ± 0.9	14 ± 6
PS	28.1	56.5	43.8	56.8	36.3	45.5
51-60						
MV ± SD	70 ± 17	298 ± 42	362 ± 101	8.5 ± 1	1.9 ± 1.6	8 ± 4
PS	27.2	49	50	59.8	41.4	19.9
Total						
MV ± SD	77 ± 23	303 ± 57	334 ± 124	7.8 ± 1.5	2 ± 1.2	16 ± 14
PS	33.6	51.5	43.8	52.9	44	54.1

MV ± SD: mean value ± standard deviation; PS: percentile score.

Table 2. The analyses of the patients whose values were outside the normal ranges

Parameters	Lower than LLNR				Higher than HLNR				Total OLNR	
	n	%	MV ± SD	MV/LLNR	n	%	MV ± SD	MV/HLNR	n	%
Iron	12	4.5	29 ± 5	0.73	NA	NA	NA	NA	12	4.5
IBC	NA	NA	NA	NA	12	4.5	453 ± 28	1.13	12	4.5
Vitamin B_{12}	5	1.9	114 ± 12	0.85	12	4.5	725 ± 98	1.23	17	6.4
Folate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TSH	4	1.5	0.2 ± 0.1	0.74	9	3.4	6 ± 2.2	1.43	13	4.9
Prolactin	NA	NA	NA	NA	14	5.3	38 ± 12	1.42	14	5.3

MV ± SD: mean value ± standard deviation; LLNR: lowest limit of the normal range; HLNR: highest limit of the normal range; OLNR: outside the limits of the normal range; NA: non-applicable.

had either low or high TSH values were further analyzed for their free T_3 and T_4 values, and all were found in normal ranges. Therefore, these TSH values were considered normal and no medication was prescribed for them. Furthermore, the patients who had solitarily higher vitamin B_{12} levels than HLNR were not prescribed any medication. Because some patients had more than one abnormal value needing medication, they were given more than one medication. Totally, 25 (9.4%) patients had one or more medications.

Two hundred and nine patients came to the second visit after the 3-month treatment period. Of these patients, 19 (9.1%) stated that hair shedding ceased totally, 156 (74.6%) diminished to some extent, and 34 (16.3%) continued as before. The number of patients who had medication(s), namely who had abnormal value(s), in these groups, was 2, 19, and 4; and their ratios to the patients in each group were 10.5%, 12.2%, and 11.8%, respectively.

Discussion

Previously, it was declared that the tendency to ATE was highest in the third decade, probably due to more

frequent health changes, such as pregnancy and deliveries, tubal ligations, starting and stopping oral contraception, menorrhagia associated with fibroids, and extreme weight fluctuations due to pregnancies[3]. In the current analysis also, among the age groups, the highest patient number belonged to the 21-30 group, that is, the third decade of life (Fig. 1).

Considering the mean values, all parameters in our study were found in normal ranges for both the entire patient population and age groups (Table 1). Furthermore, it should be emphasized that the PSs of all parameters were around 50%, suggesting a normal distribution, except for iron. The relatively low values of iron PSs might be due to the ethnic tendency of Turkish women toward lower serum iron values[12,13]. However, due to normal mean values, it should be considered that none of the analyzed parameters can directly be accused as the cause of the hair sheddings. On the other hand, in addition to the relatively low numbers of patients whose one or more values were outside the normal ranges, it was found that divergence ratios of their values from LLNR and HLNR were also quite low (Table 2). Therefore, it might be suggested that even for the individual patients whose values were outside the normal ranges, it was quite probable that their complaints were not related to these mild abnormal values. The comparable ratios of the patients who had medications (that is, the patients with abnormal values) in all three groups, as 10.5%, 12.2%, and 11.8%, whether declared the shedding had stopped, diminished, and continued, respectively; might also suggest that the abnormal values had no role in their complaints.

In ATE, fear and stress usually arise from the inability to comprehend that a completely healthy person can still have hair loss[2]. In general, patients with this complaint often believe that there is a terrible disease sneaking internally, causing hair loss despite repeated normal laboratory results and no other symptoms of any kind[3]. The characteristic wording in such cases is: “I always had a full head of hairs and now I am losing them by the handful.” Actually, the typical patient is a lady who still has a “full head of hairs”[4]. Patient education is important in disease management. Treatment for ATE is primarily reassurance and counseling. An assurance that ATE will not lead to baldness is quite helpful[3]. In our experiences, it also works well to comfort the patient by emphasizing that shedding itself is not important if there is no rarefaction or thinning of the hairs, as the body compensates for the shedding. Enthusiastic management and observation are usually appropriate as shedding is expected to cease within three to 6 months[2]. Compatible with these reports, at the end of 3rd month, 83.7% of our patients declared their shedding had ceased or diminished to some extent.

There is no sufficient evidence to indicate micronutrients and vitamin prescription for telogen effluvium. An old tradition incriminates the deficiency of iron for hair loss[4], but its role during the hair cycle has not been well studied and there are contradicting reports on the efficacy of the replacement of iron on the outcome of telogen effluvium. Indeed, large double-blind placebo-controlled trials are required to determine the effect of specific micronutrient supplementation on hair growth in those with both micronutrient deficiency and non-scarring alopecia to establish any association between them[10]. However, in our opinion, although there is insufficient data for any kind of supplementation for this condition, the expectations of the patients from the physicians are so great that it will be wise to prescribe some supplements, at least for their placebo effects. Otherwise, the feeling of dissatisfaction may urge the patients to seek other advices. Therefore besides prescribing the medications for the parameters that we found deficient in biochemical analysis, we additionally prescribed zinc and vitamin E supplements to all patients whether they had any deficiency for the searched parameters or not. Zinc and vitamin E were selected because of their anti-oxidant effects[14,15]. Vitamin E consists of fat-soluble compounds known as tocopherols and tocotrienols which function by scavenging peroxyl radicals[16]. Eight months of supplementation with 50 mg of mixed tocotrienols and 23 IU of α-tocopherol resulted in a 34.5% increased hair count in 38 patients with hair loss, compared to a 0.1% decrease with placebo[17]. Zinc has an essential role in both the structure and function of a range of proteins, transcription factors, enzymes, and hormone receptor sites[18]. However, there are conflicting data from the studies, while some of them concluded that zinc level was significantly lower in telogen effluvium patients[19,20], some others declared no statistical difference between patients and controls[21,22]. In the current study, of course, we do not have any evidence of whether they had any effect on the patients and if affected, whether that was due to their anti-oxidant and other relevant features, placebo effects, or both.

Scalp hair is an important accessory of humans and the apprehension of shedding may have deep impacts on the patients’ emotions. It generally incites more intensive distress than its objective severity and for some patients, the emotional burden of hair shedding may be

comparable to a life-threatening disease. Therefore, even if the patient has no visible signs but anxiety, the physician should not underestimate the complaints of these patients. Otherwise, it is quite probable that they will attempt to find a new physician or carry out the advices of laypeople. Initially, when the patient first referred with hair shedding complaint that commenced recently, after an incomprehensive biochemical blood test regarding the likely responsible hormones and vitamins/minerals, the reassurance of the patient by stating the benign prognose that the shedding would cease up to 6 months, will soothe the patient. Even if no abnormality is found in the test results, it is strongly recommended to prescribe some supplements due to the emotional dissatisfaction and vulnerability of these patients. Although they are extremely frustrated, if these patients are helped in an understanding and expectant way, often they are quite grateful.

Conclusions

Considering the normal mean values, low divergence ratios, and low ratios of abnormal values in the whole patient population; none of the analyzed parameters in the current study can directly be accused as the cause of the hair sheddings. In ATE the cause remains unknown in many cases and the patients generally refer without any objective sign, but with deep frustration. Treatment for ATE is primarily reassurance and counseling. Although there is insufficient data for any kind of supplementation for this disorder, the expectations of the patients from the physicians are so great that it will be prudent to provide some supplements, at least for their placebo effects. An enthusiastic management and observation are usually appropriate, as shedding is expected to cease within three to 6 months.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

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

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

Right to privacy and informed consent. The authors have obtained 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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CASE REPORT

Mutation of POGLUT1 in Galli-Galli disease: clinical, dermoscopy, and histopathology for the diagnosis

Mutação POGLUT1 na doença de Galli-Galli: a clínica, a dermatoscopia e a histopatologia

Dora Mancha[1], Rita Pimenta[2], Luís Soares-de-Almeida[1,3,4], and Paulo Filipe[1,3,4]*

[1]Dermatology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte EPE, Lisbon; [2]Department of Dermatology, Hospital Garcia de Orta E.P.E., Almada; [3]Faculdade de Medicina da Universidade de Lisboa, Dermatology Universitary Clinic, Lisbon; [4]Faculdade de Medicina, Dermatology Research Unit, Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon. Portugal

Abstract

Dowling-Degos disease (DDD) is an uncommon genodermatosis. The most closely associated disorder is Galli-Galli disease (GGD). Both conditions are considered on the same disease spectrum, with the differentiating factor being the presence of acantholysis in GGD. A 51-year-old female with a 21-year history of pruritic eruption in flexural areas progressing to the trunk and limbs presented to our dermatology consult. Physical examination revealed reddish-to-dark brown hyperkeratotic papules and reticulated confluent macules. Dermoscopy showed irregular star-shaped brown mottled areas and yellow-brown polygonal structures. Histopathology confirmed features consistent with GGD. Genetic screening identified a mutation in the POGLUT1 gene. Treatment with topical clobetasol propionate 0.05% and oral antihistamines decreased pruritus, but the skin eruption persisted. We present a rare case of GGD describing clinical, genetic, dermoscopy, and histopathological features. Clinico-pathological correlation and good cooperation between dermatologists and histopathologists are essential to make the correct diagnosis of GGD.

Keywords: Acantholysis. Dowling-Degos. Galli-Galli. Genodermatosis. Hyperpigmentation. Reticulated.

Resumo

A doença de Dowling-Degos (DDD) é uma genodermatose rara, associada à doença de Galli-Galli (GGD). O fator de diferenciação entre as duas doenças é um critério histopatológico com a presença de acantólise no caso da GGD. Mulher de 51 anos, fototipo de Fitzpatrick II, recorreu à consulta de Dermatologia por uma dermatose generalizada e pruriginosa com 21 anos de evolução, com início nas pregas e progressão o tronco e membros. Ao exame objetivo observaram-se máculas e pápulas, castanho-alaranjadas, confluentes, de aspecto reticulado que predominavam no tronco e membros. A dermatosocopia das lesões mostrou áreas irregulares em estrela de coloração castanha e estruturas poligonais amareloacastanahdas, circundadas por halos esbranquiçados. A biópsia cutânea foi compatível com GGD. O estudo genético identificou uma mutação no gene POGLUT1. Este artigo ilustra um caso raro de GGD, descrevendo suas características clínicas, genéticas, dermatoscópicas e histopatológicas. A correlação clinicopatológica é essencial para o diagnóstico de GGD.

Palavras-chave: Acantólise. Dowling-Degos. Galli-Galli. Genodermatose. Hiperpigmentação. Reticulada.

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

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Introduction

Reticulate pigmentary disorders include a variety of diseases that exhibit significant clinical overlap. Dowling-Degos disease (DDD), as the main representative, is a rare autosomal dominant genodermatosis characterized by progressive pigmented lesions primarily involving large body folds[1]. Galli-Galli disease (GGD) is characterized by the association of DDD with an acantholytic dermatosis of the spectrum Darier, Hailey-Hailey, and Grover diseases[2,3]. It was first recognized by Bardach, Gebhart, and Luger in 1982[2]. Only a few patients with this disease and genetic analysis have been reported (Table 1). Herein, we report a case of a female patient diagnosed with GGD, confirmed by genetic analysis, pointing out the clinical, dermoscopy, and histopathological aspects.

Clinical case

A 51-year-old female patient presented to our dermatology consult with a 21-year history of a pruritic eruption starting in the flexural areas with progression to the trunk and limbs. There was no personal or family history of skin disease. Physical examination revealed reddish-to-dark brown hyperkeratotic papules and reticulated confluent macules scattered on the trunk and upper and lower extremities (Fig. 1). Dermoscopy of the lesions showed irregular star-shaped brown mottled areas and yellow-brown polygonal structures surrounded by whitish haloes (Fig. 2A). At this point, we considered the following diagnostic hypotheses: Dowling-Degos disease, Galli-Galli disease, transient acantholytic dermatosis, and Darier's disease. Histopathological examination of a leg lesion skin biopsy revealed focal acantholytic dyskeratosis and elongated rete ridges down-growing into the dermis (Figs. 2B and D). Clinical, dermoscopy, and histopathology features were compatible with GGD. Genetic screening found the c.3G>C, p(Met111e) mutation on the POGLUT1 gene, confirming our clinicopathological diagnosis. Treatment was attempted with topical clobetasol propionate 0.05% and oral antihistamines. The patient's pruritus decreased, but the skin eruption has not resolved.

Discussion

DDD is an uncommon genodermatosis; < 100 cases have been reported in the literature[4]. The most closely associated disorder is GGD, with both conditions being considered on the same disease spectrum[3-6]. GGD can be differentiated from DDD histologically, with the differentiating factor being the presence of acantholysis in GGD[4-6]. Thus, GGD is considered an acantholytic variant of DDD. The disease's onset age varies, ranging from early adolescence to late adulthood[6]. The central genes implicated in DDD/GGD pathogenesis are KRT5 (keratin 5 gene), POGLUT1 (protein O-glucosyltransferase 1), POFUT1 (protein O-fucosyltransferase 1), and PSENEN (presenilin enhancer protein 2 gene)[4,5]. Our patient presented a mutation on POGLUT1, an essential regulator of Notch signaling. Mutations in POGLUT1 result in aberrations in Notch signaling, leading to abnormal pigmentation and keratinocyte morphology[5]. The mode of inheritance is thought to be autosomal dominant with variable penetration, but sporadic cases have also been observed, such as in our patient[6].

Clinically, DDD/GGD presents with reticulate hyperpigmentation of the flexures; the main sites of involvement are the axilla, inguinal folds, submammary folds, and the neck[4,6]. Although the lesions are usually asymptomatic, they may occasionally be associated with pruritus[4]. At the physical examination, the lesions appear round-to-oval hyperpigmented lentigo-like macules[3,4]. Our patient presented a disseminated and pruritic dermatosis involving the trunk and extremities. Clinically, differential diagnoses include reticulate hyperpigmentation disorders such as Haber syndrome, acropigmentation of Dohi, and reticulate acropigmentation of Kitamura, that differ from GGD in clinical factors such as age of onset

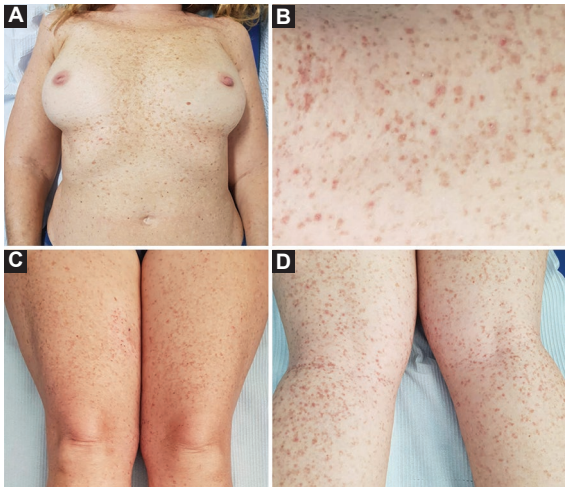

Figure 1. A: reddish-to-dark brown hyperkeratotic papules and reticulated confluent macules scattered on the trunk and upper extremities. **B-D:** numerous hyperkeratotic, red-brown, flat-topped papules, some with overlying peripheral crust, with a background of lentigo-like macules on lower extremities.

Table 1. Literature review. Galli-Galli disease with genetic analysis

Author/year	Patients (age/sex)	Clinical description	Genetic analysis	Histopathology	Dermoscopy	Treatment
Voth et al. (2011)[11]	68/M	Chronic pruritic erythematous hyperkeratotic papules of axillae, neck, trunk, and groin	c. 418dupA KRT5 gene	Lentiginous changes Suprabasal acantholysis	-	Topical corticosteroids (no improvement) Topical antibiotics (no improvement) Oral antihistamines (no improvement) Erbium: YAG laser (dyspigmentation)
Reisenauer et al. (2014)[7]	48/F	Pruritus and hyperpigmented erythematous macules and thin papules along the flexor surfaces of her arms, her upper back and neck, axillae, and inframammary areas	*KRT5* (c. 38dupG; Ser14GlnfsTer3)	Lentiginous changes Suprabasal acantholysis	-	Tretinoin cream 0-025% cream (pruritus worsened, irritation) Hydrocortisone 2 a 5% and emollients as needed (no response reported)
Lõrincz et al. (2018)[12]	74/M	Hypopigmented papules, hyperpigmented macules of neck, trunk, and flexor extremities	c. 418dupA KRT5 gene	Lentiginous changes Suprabasal acantholysis		Acitretin, 25 mg every other day to daily (inflammatory eruption and pigmentation improved)
Rundle, Ophaug & Simpson (2020)[10]	77/F	Widespread eruptions of pruritic crusted and scaling pink papules and tan macules, which started on the thighs and later progressed to involve the neck, trunk, flexor, and extensor surfaces of the extremities	Nonsense mutation in POGLUT1, p.(Arg218*); c. 652>T	Lentiginous changes Suprabasal acantholysis, dyskeratosis	-	Topical corticosteroids (no improvement) Doxepin, 20 mg nightly (no improvement) Acitretin, 10-25 mg/d (pruritus and papular eruption resolved)
Current report (2023)	55/F	Reddish-to-dark brown hyperkeratotic papules and reticulated confluent macules scattered on the trunk and upper and lower extremities	c. 3G>C, P (Met111e) mutation on POGLUT1	Lentiginous changes Suprabasal acantholysis, dyskeratosis	Irregular star-shaped brown mottled areas and yellow-brown polygonal structures surrounded by whitish haloes	Topical clobetasol propionate 0,05% and oral antihistamines. (modest improvement on pruritus; papular eruption not resolved)

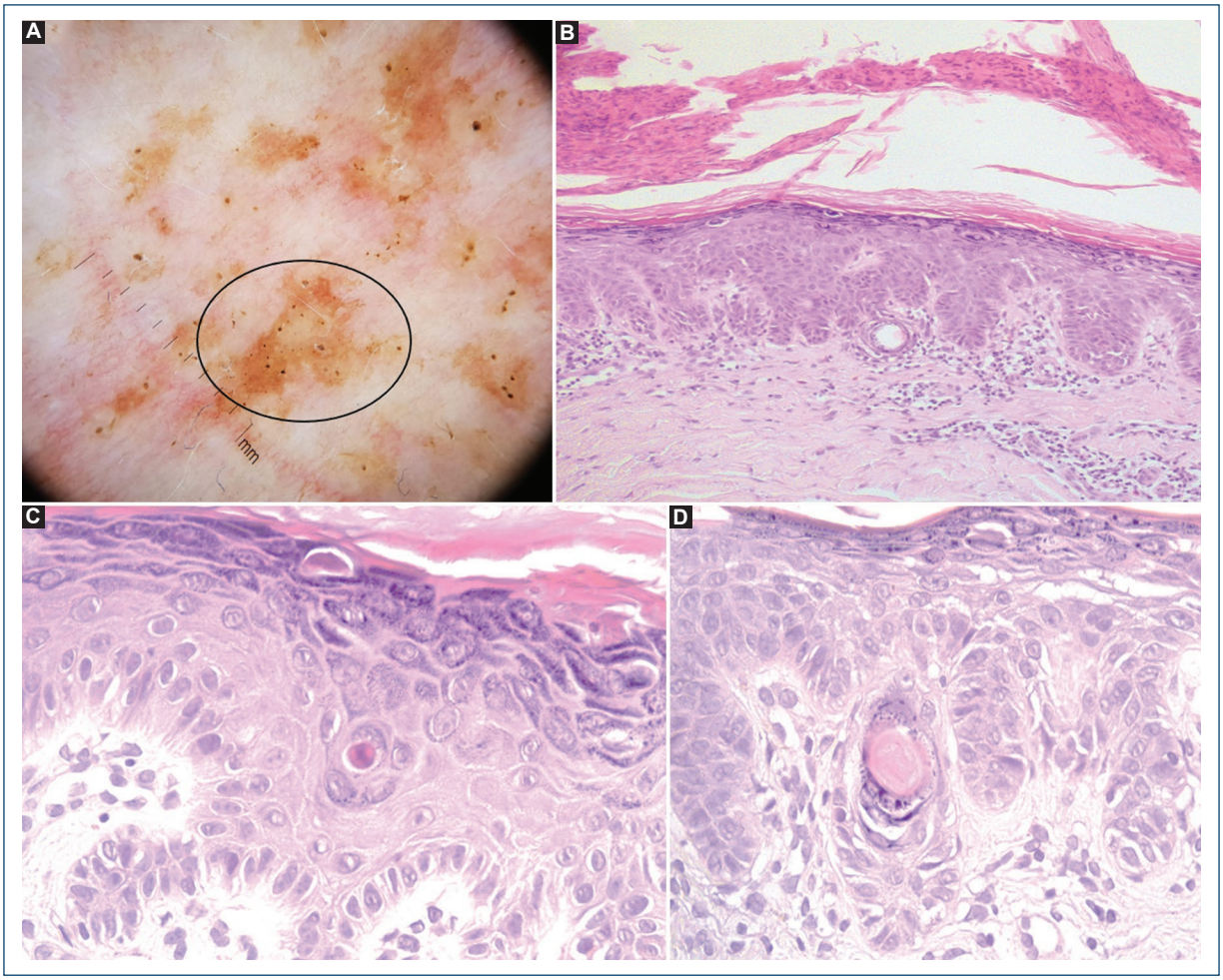

Figure 2. A: dermoscopy in polarized mode (×10 magnification) of a hyperkeratotic papule (leg): irregular star-shaped brown mottled areas (black circle) and yellow-brown polygonal structures surrounded by whitish haloes corresponding to follicular plugging and inclusion cysts; regular hairpin and dotted vessels are also visibly surrounded by whitish haloes on a pinkish background. **B:** histopathology (hematoxylin-eosin ×100) of a leg lesion skin biopsy revealed scattered suprabasal lacunae and a subcorneal cleft under a parakeratotic scale. Note the pattern of elongated, pigmented, finger-like rete ridge epidermal acanthosis and elongated rete ridges with down growth of filiform anastomosing epithelial strands. The dermis shows a dense infiltrate of predominantly lymphocytes. **C** and **D:** histopathology (hematoxylin-eosin ×400) of a lentigo-like macule biopsy revealed acantholysis, keratin plug formation, and dilatation of the follicular infundibulum with the focal formation of a pseudohorncyst.

or location of skin lesions[4-6]. Haber's syndrome is characterized by verruciformis papular lesions of the trunk and distinct facial erythema, most commonly presenting in childhood. The acropigmentation Dohi is characterized by the presence of hyperpigmented and hypopigmented pinpoints or pea-sized macules on the backs of the hands and feet. In Kitamura's disease, breaks in palmar pits, and acral hyperpigmentation can be observed, especially on the backs of hands and feet[6]. In addition, the genetic background is different. The acropigmentation of Dohi is associated with mutations in ADAR1 (adenosine deaminase, RNA-specific 1) on chromosome 1, and mutations in ADAM10, encoding a zinc metalloprotease, have recently been identified in reticulate acropigmentation of Kitamura; at present, there are no genes/gene loci associated with Haber syndrome[7].

Dermoscopy is not routinely employed for DDD/GGD diagnosis[4]. In our case, dermoscopy revealed some typical features of GGD: an irregular star-shaped brown outline on a red-brown background, follicular plugging, and inclusion cysts[4,8]. The dermatoscopic features may reflect the characteristic histology of DDD/GGD disease. The irregular brown star-shaped outline of color is created by the uneven distribution of inclusion cysts

and follicular plugging, preventing visualization of the basal layer pigment[4,8]. Thus, dermoscopy may provide essential clues for diagnosing DDD/GGD when adequately integrated with clinical data. Knowledge of such *in vivo* features can allow an early diagnosis. Moreover, the most representative skin lesion for the histopathological examination can be taken based on a dermoscopy.

The well-defined pattern of acantholysis in GGD is a unique hallmark and a distinct histopathological feature within the histomorphologic monotony of reticulate pigmented disorders[6]. Histologic features of GGD include acantholysis and seborrheic keratosis-like changes, including follicular hyperkeratosis and epidermal acanthosis with down growth of filiform anastomosing epithelial strands with basal hyperpigmentation[3,4]. The histologic differential diagnosis for GGD includes entities characterized by focal acantholysis, namely Darier disease, Hailey-Hailey disease, and Grover disease[3,4,6].

The treatment of DDD/GGD is complex, and a standard treatment strategy has yet to be established[4]. First, patients must be advised to avoid friction through clothing and to use sun-protective measures to prevent the worsening of hyperpigmentation. Reported therapeutic options include topical and systemic corticosteroids, topical retinoids, cyclosporine, and UVB phototherapy, although most of these interventions have shown limited success[4,9,10]. Intense pulsed light therapy and laser devices (Er: YAG; Q-switched Nd: YAG) have been used with acceptable results[4,9,11]. Ablating the pathologic epidermis and triggering regeneration of a new epidermis from the interfollicular epithelium may help resolve the clinical lesions[4]. Unfortunately, this condition is progressive, and most treatment modalities fail to resolve the lesions completely[4,10]. In our case, the patient refused treatment with oral retinoids and UVB phototherapy. The knowledge about the benign nature of the dermatosis was reassuring, and she was satisfied with pruritus control.

GGD and DDD are inherited skin diseases with variable progressive course. They are of benign and harmless behavior but esthetically annoying[6]. We present a rare case of GGD describing clinical, genetic, dermoscopy, and histopathological features. Clinicopathological correlation and good cooperation between dermatologists and histopathologists are essential to make the correct diagnosis of GGD.

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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

Hutchinson's sign in congenital nail matrix nevus

Sinal de Hutchinson no nevo congénito da matriz ungueal

Ana Ferreirinha[1], Maria C. Fialho[1], Pedro M. Garrido[2], Joaninha Costa-Rosa[3], and Cecília Moura[2]*

[1]Department of Dermatology and Venereology, Hospital de Santo António dos Capuchos, Centro Hospitalar Universitário de Lisboa Central, Alameda Santo António dos Capuchos; [2]Department of Dermatology and Venereology, Instituto Português de Oncologia de Lisboa; [3]Department of Anatomic Pathology, Instituto Português de Oncologia de Lisboa. Lisbon, Portugal

Abstract

Congenital nail matrix nevi (NMN) are a rare cause of melanonychia that may present with irregularity, asymmetry, and multicomponent pigmentation posing diagnostic challenges with subungual melanoma. We report a case of a 49-year-old female with longitudinal melanonychia and a 1-month recent pigmentation in the proximal nail fold. This sign is traditionally associated with malignancy, which further complicates the differentiation from acral melanoma. Therefore, a nail matrix biopsy was performed. Histopathologic examination revealed a nail matrix nevus. This procedure is crucial in suspicious cases, despite the risk of nail dystrophia. The evolution of these nevi into adulthood and their potential malignancy remains unclear, emphasizing the need for continued research and surveillance. This case highlights that congenital NMN often present with clinical and dermoscopic features of concern, mirroring those observed in subungual melanoma.

Keywords: Congenital melanocytic nevus. Congenital nail matrix nevus. Dermoscopy. Hutchinson's sign. Longitudinal melanonychia. Subungual melanoma.

Resumo

Os nevos congénitos da matriz ungueal são uma causa rara de melanoníquia que pode apresentar-se com irregularidade, assimetria e pigmentação multicomponente, o que dificulta o diagnóstico diferencial com melanoma subungueal. Descrevemos o caso de uma mulher de 49 anos com melanoníquia longitudinal que progrediu com pigmentação na prega ungueal proximal. O sinal de Hutchinson está frequentemente associado a malignidade, o que dificulta ainda mais a diferenciação com o melanoma acral. Realizou-se uma biópsia da matriz ungueal, cujo exame histopatológico foi compatível com nevo da matriz ungueal. Esta abordagem é crucial em casos suspeitos, apesar do risco de distrofia ungueal. A evolução destes nevos até à idade adulta e o seu potencial de malignidade permanecem pouco claros, enfatizando a necessidade de vigilância contínua. Este caso realça que os nevos congénitos da matriz ungueal se apresentam frequentemente com características clínicas e dermatoscópicas suspeitas, que podem mimetizar as observadas no melanoma subungueal.

Palavras-chave: Dermatoscopia. Melanoma subungueal. Melanoníquia longitudinal. Nevo melanocítico congénito. Nevo congénito da matriz da unha. Sinal de Hutchinson.

***Correspondence:**
Ana Ferreirinha
E-mail: ana.ferreirinha@chlc.min-saude.pt

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Introduction

Nail matrix nevi (NMN) are often considered in the differential diagnosis of acral melanoma, as they both present with melanonychia as a common feature[1]. In fact, congenital NMN frequently combine semiologic features of irregularity and asymmetry with a multicomponent pigmentation of the nail plate and surrounding tissue that could suggest malignancy[1]. Despite the invasive nature and emotional distress associated with nail matrix biopsy, it is crucial in cases with a high level of suspicion[1,2]. In this context, we report a case of congenital nail matrix nevus with recent suspicious changes, exploring its clinical and dermoscopic features.

Case report

A 49-year-old female patient was referred to our dermatology department due to a 1-month evolution of pigmentation in the proximal nail fold, associated with a longstanding longitudinal melanonychia on the second toe's nail.

The patient reported having melanonychia since the 1st year of life and that it had not changed until a month before.

Physical examination showed light brown irregular longitudinal melanonychia covering over two-thirds of the nail without dystrophy, along with irregular monochromatic dark brown pigmentation in the proximal nail fold (Fig. 1). Dermoscopy revealed irregular light and dark brown longitudinal microlines in the dorsal nail plate and dark brown diffuse irregular pigmentation in the proximal nail fold (Figs. 2A and B).

Recent changes prompted a nail matrix biopsy. The nail matrix biopsy was performed under local anesthesia with a proximal digital block. Subsequently, a tourniquet was applied, the proximal nail fold was retracted, and the nail plate was avulsed (Fig. 3). A tangential incisional biopsy was performed, and finally, the retracted fold and the avulsed nail plate were sutured.

Histopathological examination revealed hyperpigmentation of the basal layer of the epidermis and coexisting melanophages in the dermis, without melanocytic junctional proliferation or dysplasia of the nail matrix, consistent with a nail matrix nevus (Fig. 4).

At the 3-month follow-up, the patient did not exhibit new changes in the nail or periungual tissue, and no dystrophy was observed.

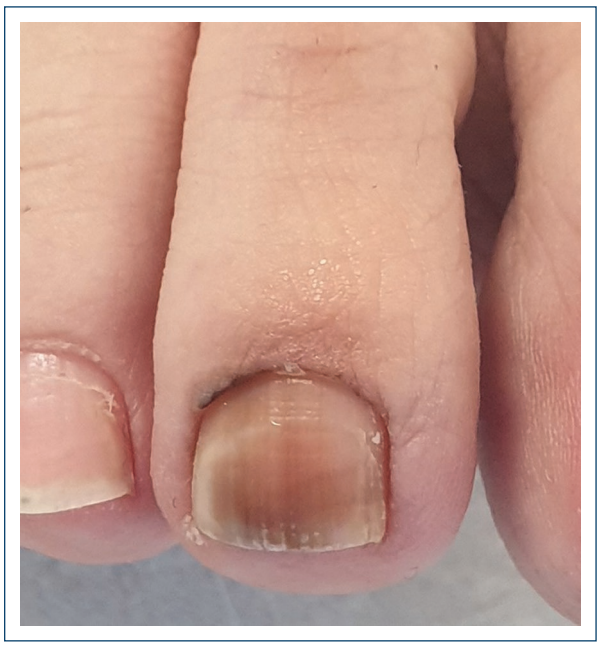

Figure 1. Clinical findings of the nail plate – light brown irregular longitudinal melanonychia covering over two-thirds of the nail without dystrophy, along with irregular dark brown pigmentation in the proximal nail fold.

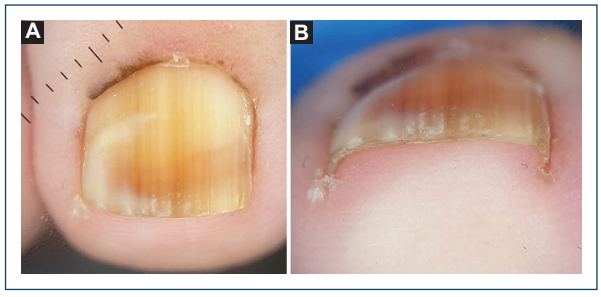

Figure 2. Dermoscopy of the nail. **A:** dermoscopy view of the nail plate: irregular light and dark brown longitudinal microlines with blurred lateral borders, covering over two-thirds of the nail plate, and dark brown diffuse irregular pigmentation in the proximal nail fold.
B: dermoscopy view of the distal edge of the nail plate: irregular light and dark brown longitudinal microlines in the dorsal nail plate without any pigmentation in the hyponychium.

Discussion

Congenital NMN are rare, with limited documented cases described in the literature[1]. They frequently exhibit clinical and dermoscopic distinctive features such as irregularity, asymmetry, and multicomponent

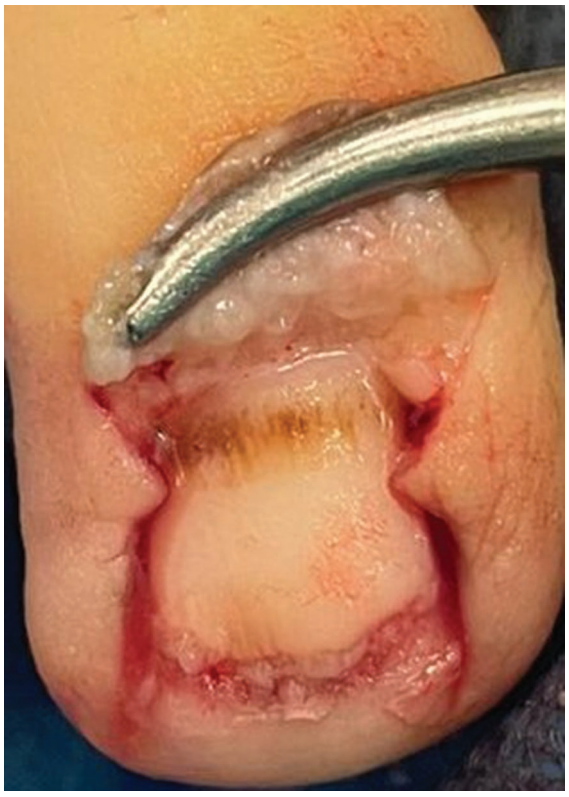

Figure 3. Intraoperative view of the nail matrix biopsy showing the light and dark brown fibrillar pattern of the nail matrix.

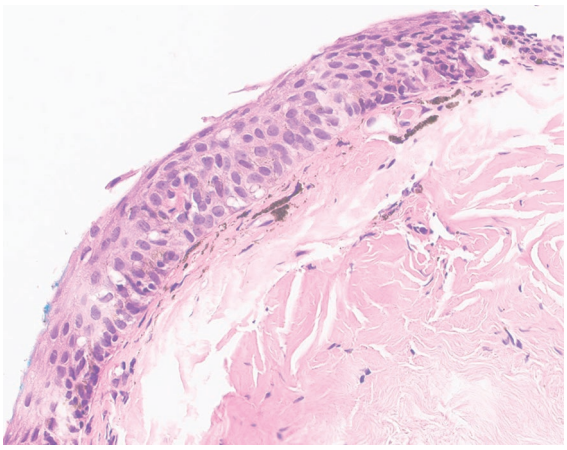

Figure 4. Histopathology of the nail matrix – hyperpigmentation of the basal layer of the epidermis and coexisting melanophages in the dermis, without melanocytic junctional proliferation or dysplasia (hematoxylin and eosin stain).

pigmentation affecting the nail plate with or without involvement of the periungual tissues, raising concerns about potential malignancy[1-3]. The main clinical and dermoscopy feature of congenital NMN is the irregular pattern, defined by longitudinal microlines, irregularity in width, space, color, triangular shape, polychromasia, and irregular periungual pigmentation[1]. Furthermore, the most prevalent dermoscopic pattern of the periungual pigmentation has been described as a distal fibrillar ("brush-like") pattern[1].

The notable characteristic of melanonychia extending into the periungual tissues, known as Hutchinson's sign, is traditionally associated with acral melanoma[2,3]. In addition to acral melanoma and congenital NMN, other differentials associated with Hutchinson's sign include ethnic variations, trauma, systemic diseases, and drug adverse effects[2,3].

Due to the rarity of congenital matrix nevi, there is a lack of consensus regarding their management. However, in the majority of congenital NMN cases, conservative management suffices, with clinical follow-up, including clinical photography and dermoscopy[2]. Performing a nail matrix biopsy is mandatory in suspicious cases, although it may have a risk of permanent scarring[1,4,5].

Histopathologic analyses of nail matrix biopsies in congenital NMN are infrequent in the literature. Nevertheless, some cases have been described as junctional NMN or as functional melanocytic activation[1]. In our case, the biopsy showed features of melanocytic activation. In addition to congenital NMN, other causes of melanocytic activation include pregnancy, chronic trauma, nail-biting, drug adverse effects, and systemic diseases[4], none of which were present in our case.

Aggressive procedures, such as complete excision involving the entire length of the nail matrix, are reserved for situations where melanoma cannot be ruled out even after an expert review of clinical and histopathologic findings[2]. However, subungual melanoma cases arising in congenital NMN are exceptionally rare, casting doubt on the accuracy of diagnoses[1,6]. Furthermore, there is currently no data in the literature regarding the evolution of congenital NMN into adulthood and their risk of malignant transformation.

Conclusion

This case highlights that congenital NMN frequently manifest clinically and dermoscopically alarming characteristics, mirroring those observed in subungual

melanoma. This resemblance is particularly evident in the presence of the Hutchinson's sign. Notably, the diagnostic criteria established for adult subungual melanoma may not be directly applicable or reliable when evaluating congenital NMN.

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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

Pigmented cutaneous metastasis of breast carcinoma: florid case with zosteriform distribution

Metástase cutânea pigmentada de carcinoma mamário: caso exuberante e com distribuição zosteriforme

Francilene M. Peçanha[1], Melissa de S. Melo-Cavalcante[1], Virgínia V. Figueiras[1], Monique F. dos Reis[1], Flávio L. Dantas-Portela[2], and Luciana Mendes-dos Santos[1]*

[1]Department of Dermatology, Doctor Heitor Vieira Dourado Tropical Medicine Foundation; [2]Department of Pathology and Legal Medicine, Getúlio Vargas University Hospital. Manaus, Amazonas, Brazil

Abstract

This case report presents a rare manifestation of a pigmented cutaneous metastasis of breast carcinoma with a zosteriform distribution. A 77-year-old woman, previously diagnosed with invasive ductal carcinoma of the breast, exhibited pigmented lesions resembling shingles on the left thoracodorsal region. Dermoscopic and histopathological examinations confirmed invasive carcinoma of mammary origin associated with melanocytic colonization. The zosteriform pattern, though rare, has been reported in cases of cutaneous metastasis from breast cancer. Treatment options include addressing the primary tumor and direct approaches such as surgery or radiotherapy for skin lesions. This report highlights the importance of clinical suspicion, histopathological evaluation, and immunohistochemical examinations for accurate diagnosis, enabling timely and appropriate treatment for improved patient outcomes.

Keywords: Breast neoplasms. Neoplasm metastasis. Skin pigmentation. Pathology. Immunohistochemistry.

Resumo

Este relato de caso apresenta uma manifestação rara de metástase cutânea pigmentada de câncer de mama com distribuição zosteriforme. Uma mulher de 77 anos, previamente diagnosticada com carcinoma ductal invasivo de mama, apresentava lesões pigmentadas semelhantes a herpes-zóster na região toracodorsal esquerda. Os exames dermatoscópico e histopatológico confirmaram carcinoma invasivo de origem mamária associado à colonização melanocítica. O padrão zosteriforme, embora raro, já foi relatado em casos de metástases cutâneas de câncer de mama. As opções de tratamento incluem abordar o tumor primário e abordagens diretas, como cirurgia ou radioterapia para lesões cutâneas. Este relatório destaca a importância da suspeita clínica, avaliação histopatológica e exames imuno-histoquímicos para um diagnóstico preciso, permitindo um tratamento oportuno e apropriado para melhores resultados dos pacientes.

Palavras-chave: Neoplasias mamárias. Metástase neoplásica. Pigmentação da pele. Patologia. Imunohistoquímica.

***Correspondence:**
Francilene M. Peçanha
E-mail: francilenepecanha@hotmail.com

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Introduction

Breast cancer is the malignancy with the highest incidence and mortality between women worldwide[1]. These tumors may complicate with metastasis, including rare cutaneous metastasis. In fact, after melanoma, breast cancer has the highest incidence rate of cutaneous metastasis among the solid malignancies[2]. Usually, cutaneous metastasis presents as a nodular disease, even though inflammatory, cicatricial, and bullous presentations are possible[2]. Zosteriform distribution of cutaneous secondary neoplasia is a rare clinical presentation[3]. In this paper, we report a case of a florid pigmented cutaneous metastasis of breast carcinoma with a zosteriform clinical presentation.

Clinical case

A 77-year-old woman, born in Manaus, state of Amazonas, Brazil, with a previous diagnosis of invasive ductal carcinoma of the left breast in 2015, underwent a total mastectomy following chemotherapy in the same year. In 2022, she was referred to the dermatology clinic due to pigmented lesions present for 2 years, initially on the bed of the mastectomy, which progressively spread to the entire left hemithorax and ipsilateral back. During this period, the diagnosis of shingles (herpes zoster) was suggested, but the patient did not have any clinical improvement despite antiviral therapy.

Dermatological examination revealed extensive infiltrative blackish papules and plaques, with a hard consistency. There were some flaccid blisters with serohematic content. The lesion was following a zosteriform distribution in the left thoracodorsal region, more specifically dermatomes T2 through T8 (Figs. 1 and 2). No lymphadenopathies were detected at clinical examination.

The main dermoscopy findings were peripheral dots, globules and some radiating striae, with irregular distribution, over an amorphous area, in addition to areas with the appearance of a blue-white veil, suggestive of a melanocytic lesion (Fig. 3). Thorax, abdomen, and pelvis CT scan (CT-TAP) and bone scintigraphy did not show any signs of metastatic disease.

Histopathology showed atypical epithelioid neoplastic cells, arranged in cords in the superficial and deep dermis, reaching the hypodermis. The presence of intracytoplasmic melanin pigment was observed in the atypical cells located in the superficial dermis (Fig. 4A and B). The lesion was positive for AE1/AE3, ER and GATA-3. Melanocytic markers (Melan-A and S100) were negative.

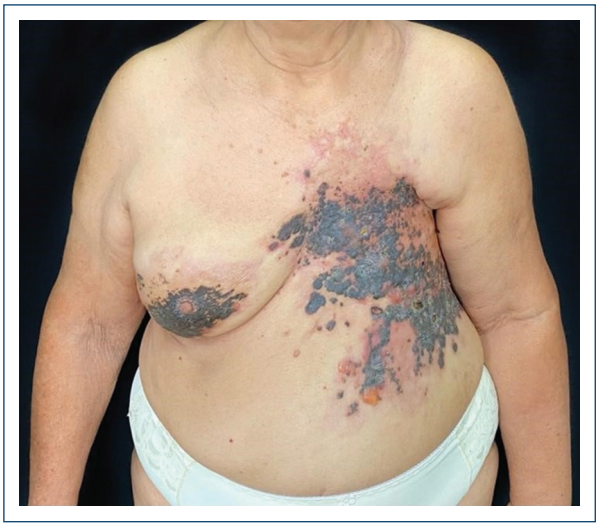

Figure 1. Extensive infiltrative blackish papules and plaques, with increased consistency, and some flaccid blisters with serohematic content.

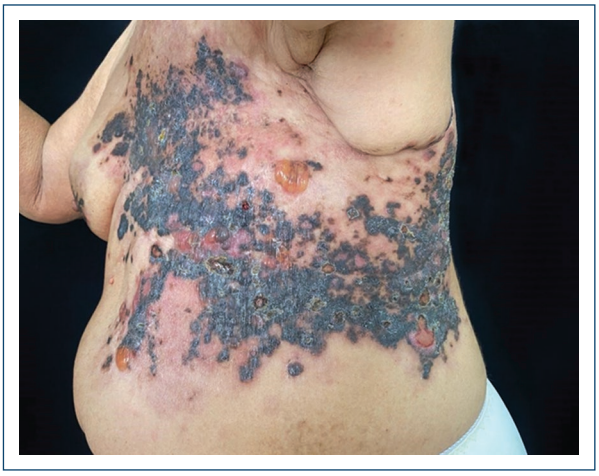

Figure 2. Zosteriform distribution pattern of skin lesions.

Based on these findings, the diagnosis of skin infiltration by invasive carcinoma of mammary origin associated with melanocytic colonization was established.

At the moment, the patient is undergoing follow-up at the oncology outpatient clinic, undergoing chemotherapy.

Discussion

First described by Azzopardi and Eusebi (1997), pigmented cutaneous metastases are rare and atypical manifestations of breast carcinoma. The lesions can mimic melanoma lesions and are generally found in the

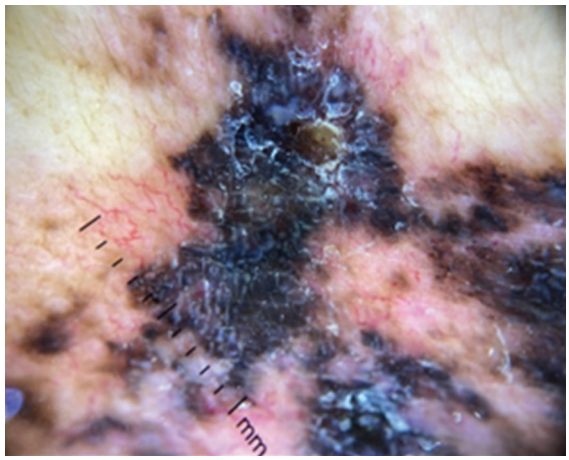

Figure 3. Dermoscopy: peripheral dots, globules, and some radiating striae in irregular distribution over an amorphous area and areas with a blue-white veil.

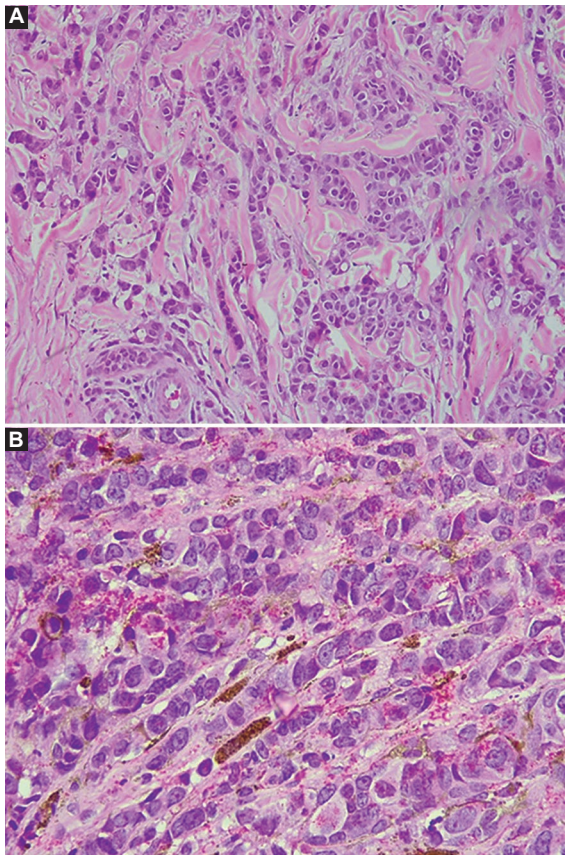

Figure 4. A: neoplastic cells with rounded, hypertrophic, hyperchromatic nuclei, with evident nucleoli, forming small nests and cords in desmoplastic stroma. H/E. Magnification = ×200. **B:** intracytoplasmatic and stromal melanin deposits. H/E. Magnification = ×400.

thoracoabdominal region, especially on the site of the scar from a previous mastectomy[3,4]. Initially, Azzopardi and Eusebi (1997) proposed that pigmentation would be related to the rupture of the basement membrane secondary to tumor invasion, determining pigment spillage, dermal melanophages, and migration of epidermal melanocytes[3]. Secretion of growth factors by malignant cells would be related with the migration and survival of these dendritic melanocytes[5].

However, cases without pagetoid involvement demand other explanations to justify the presence of melanocytes in the metastatic tumor stroma[5]. There is evidence that multipotent dermal stem cells are capable of differentiating into melanocytes. Melanoblasts residing in the bulb region of hair follicles can also differentiate into dermal melanocytes[6]. Therefore, melanocytic colonization of cutaneous metastases from breast carcinoma can also occur by melanocytes of non-epidermal origin.

The zosteriform distribution of cutaneous metastasis of breast carcinoma is rare, with few cases reported in literature, the first being described in 1933[7,8]. A review of the literature of zosteriform cutaneous metastasis showed that, among 15 total cases, four were from patients with primary breast malignancy, being the most frequent primary tumor associated with this manifestation[9]. The pathophysiological explanation to the zosteriform disposition of these metastases is not well understood, but there is some hypothesis of possible mechanisms: lymphatic dissemination of locoregional tumors, köebnerization of previous sites of varicella-zoster, iatrogenic seeding of malignant cells, and neural dissemination through dorsal ganglia[8].

Successful treatment of the primary tumor is often sufficient for regression of the skin lesions. However, a direct approach to the cutaneous lesion can help reduce tumor burden, improve quality of life, and increase functionality. Treatment modalities include direct surgical excision, radiotherapy, laser or radiofrequency ablation, cryotherapy, and alpha-interferon injections[10].

Unusual forms of cutaneous metastases from breast carcinoma, as described in this case report, become real diagnostic challenges. For such cases, clinical suspicion, associated with histopathological and immunohistochemical examinations, is essential. With an accurate diagnosis, appropriate treatment can be carried out more immediately, guaranteeing a significant improvement in the quality of life of our patients.

Conclusion

Breast cancer's rare cutaneous metastasis, such as the pigmented zosteriform type described here, poses diagnostic and treatment challenges. Understanding these manifestations is critical for accurate diagnosis and timely intervention. Multidisciplinary collaboration and advanced diagnostic tools play pivotal roles in optimizing patient care. Further research is needed to refine management strategies for such atypical presentations.

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Conflicts of interest

None.

Ethical disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance with the regulations established by those responsible for the Clinical Research and Ethics Committee and in accordance with those of the World Medical Association and the Declaration of Helsinki.

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

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

Use of artificial intelligence to generate texts. The authors declare that they did not use any type of generative artificial intelligence in writing this manuscript, nor to create figures, graphs, tables, and/or their respective captions.

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CASE REPORT

A case of anaphylaxis induced by intravenous hydrocortisone

Um caso de anafilaxia induzida por hidrocortisona endovenosa

Ana G. Lopes[1], Carmem Botelho[2], and Lise Brosseron[2]*

[1]Department of Dermatology; [2]Department of Immunoalergology. Hospital de Braga, Braga, Portugal

Abstract

Our case focuses on a 34-year-old woman, pregnant, with a history of allergic rhinitis treated with antihistamines as needed. She had no documented history of medication allergies. At 38 weeks she went into labor. Three days after delivery, she received intravenous hydrocortisone for postpartum pain management. During administration, the patient developed generalized urticaria, dysphonia, and dyspnea. She was brought to the emergency room and received intramuscular adrenaline and antihistamines with clinical improvement. Prick tests for methylprednisolone succinate 10 mg/ml and hydrocortisone succinate 10 mg/mL and 100 mg/ml were positive. In challenge testing, the patient tolerated dexamethasone and budesonide. A diagnosis of anaphylactic reaction to group A corticosteroids was made. The patient was instructed to avoid hydrocortisone, methylprednisolone, and prednisolone. Although rare, corticosteroid allergy has very important therapeutic consequences; therefore it is necessary to be alert and to offer a safe alternative to these patients demonstrating tolerance to other corticosteroids.

Keywords: Anaphylaxis. Anaphylactic reaction. Corticosteroids. Allergy. Prick test.

Resumo

O nosso caso foca-se numa mulher de 34 anos, grávida, com antecedentes de rinite alérgica tratada com anti-histamínicos em SOS. Não tinha histórico documentado de alergias a medicamentos. Às 38 semanas, entrou em trabalho de parto. Três dias após o parto, foi medicada com hidrocortisona intravenosa para o controlo da dor pós-parto. Durante a administração, a doente desenvolveu anafilaxia. Foi levada para a sala de emergência, tendo sido tratada com adrenalina intramuscular e anti-histamínicos, com melhoria clínica. Os testes cutâneos *prick* para succinato de metilprednisolona 10 mg/ml e succinato de hidrocortisona 10 mg/mL e 100 mg/ml foram positivos. Posteriormente foram realizadas provas de provocação com dexametasona e budesonida, com boa tolerância. Foi feito o diagnóstico de reação anafilática a corticosteróides do grupo A. A doente foi recomendada a evitar totalmente o uso de hidrocortisona, metilprednisolona e prednisolona. Apesar de rara, a alergia a corticosteróides tem consequências terapêuticas muito importantes; por isso é necessário estar alerta e oferecer uma alternativa segura a estes pacientes que demonstram tolerância a outros corticosteróides.

Palavras-chave: Anafilaxia. Reação anafilática. Corticosteróides. Alergia. *Prick* teste.

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

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Introduction

Anaphylaxis is a severe and potentially life-threatening allergic reaction that can be triggered by several substances and medications. Glucocorticoids, commonly prescribed in allergic reactions for their potent anti-inflammatory properties, are generally well-tolerated and considered safe. However, in rare instances, glucocorticoids themselves can become the unsuspecting culprits behind anaphylactic reactions[1]. This paper presents a rare clinical case of anaphylaxis induced by glucocorticoid administration.

Case report

Our case focuses on a 34-year-old woman, pregnant, with a history of allergic rhinitis treated with antihistamines as needed. She had no documented history of drug allergies.

During pregnancy, she was prescribed hydrocortisone cream for an irritant contact dermatitis, with resolution of the dermatosis.

At 38 weeks of gestation, the patient experienced a vaginal delivery complicated by an unintentional dural puncture for epidural analgesia. The baby was born healthy.

Three days after labor, she received intravenous hydrocortisone for postpartum pain management. During administration, within minutes, the patient developed severe dyspnea, with decreased oxygen saturation, dysphonia, and generalized urticaria. She was brought to the emergency room and was treated with intramuscular adrenaline and antihistamines with clinical improvement. Serum tryptase concentration measured 1 h after emergency treatment was 1.7 ng/mL (normal range 0-11.4 ng/mL).

The patient was referred to the imunoallergology department for further study. Skin prick tests, intradermal skin tests, and challenge tests were performed.

Prick tests for aeroallergens were positive for *Dermatophagoides pteronyssinus* (10 mm), *Dermatophagoides farinae* (10 mm), *Lepidoglyphus destructor* (10 mm), cat dander (10 mm), dog dander (6 mm), grass pollen (6 mm), and Artemisia vulgaris (10 mm).

Prick tests for methylprednisolone succinate 10 mg/ml and hydrocortisone succinate 10 mg/mL and 100 mg/ml were positive (4 mm, 3 mm, and 4 mm, respectively), whereas those for dexamethasone sodium phosphate 4 mg/ml, budesonide 0.25 mg/ml, and latex were negative (Fig. 1).

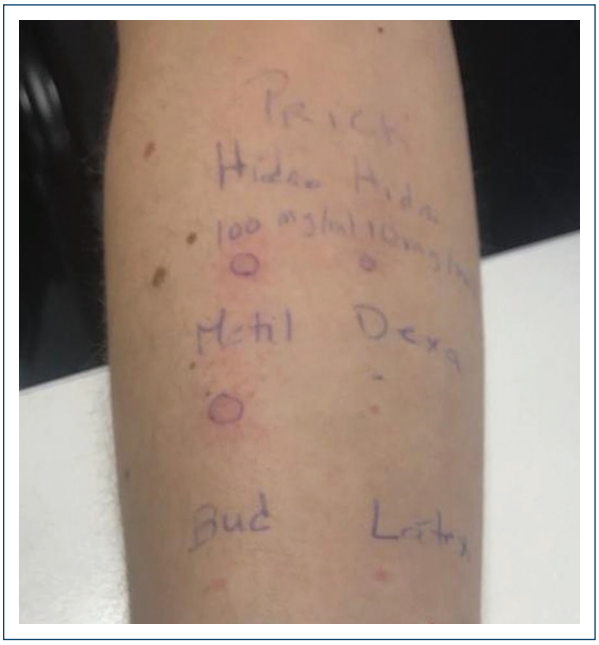

Figure 1. Prick tests positive for methylprednisolone succinate 10 mg/ml and hydrocortisone succinate 10 mg/mL and 100 mg/ml.

Intradermal skin tests for dexamethasone sodium phosphate 0.004 mg/ml and budesonide 0.0025 mg/ml were negative.

A diagnosis of anaphylactic reaction to group A corticosteroids was made. The patient was instructed to completely avoid hydrocortisone, methylprednisolone, and prednisolone.

In challenge testing with nasal budesonide and oral dexamethasone, the patient showed no reaction, making these a safe alternative corticosteroid.

Discussion

Glucocorticoids, such as prednisone and hydrocortisone, are widely used in the management of various inflammatory and immunological disorders, including anaphylaxis. Despite their extensive use, reports of anaphylaxis resulting directly from glucocorticoids remain infrequent, making this clinical case of importance. Anaphylaxis secondary to glucocorticoids that contain succinate esters is reported to have a prevalence of 0.3% and about 0.1% of parenteral administrations[2,3].

The mechanisms underlying glucocorticoid hypersensitivity reactions are not completely understood. These reactions may occur due to an abnormal immune response to glucocorticoids or their excipients. Genetic

predisposition, previous exposure to glucocorticoids, and underlying immune disorders can play a role.

Glucocorticoid hypersensitivity reactions can manifest in various ways and the severity of symptoms can range from mild to severe. They can be divided into two categories: immediate reactions, occurring within 1 h of drug administration, and non-immediate reactions, manifesting more than an hour after drug administration. The latter group is the most common, with allergic contact dermatitis following topical corticosteroids application being the most frequently reported[4].

Signs and symptoms of immediate hypersensitivity to glucocorticoids include pruritus, rash, hives, angioedema, shortness of breath, coughing, nausea, vomiting, abdominal pain, fever, and, in rare cases, anaphylactic shock. Hypersensitivity reactions have been reported following intravenous, intramuscular, oral, intra-articular, epidural, and topical administration[5-8]. In this case, the patient developed anaphylaxis within minutes of intravenous administration.

Diagnosing glucocorticoid hypersensitivity reactions can be challenging. Prick, patch, intradermal, and challenge testing with glucocorticoid preparations can be performed to confirm hypersensitivity, identify potential cross-reactivity with other medications, and provide long-term management strategies[9]. Prick testing is suggested initially, and, if negative, intradermal testing is then performed, and, in many cases, a challenge testing is also needed[7,9]. Prick and intradermal test results are considered positive when the wheal produced is at least 3 mm larger than that elicited by normal saline control[9]. In this case, we performed prick tests, which confirmed the diagnosis, and intradermal testing followed by challenge testing to identify safe alternatives.

Based on stereochemistry, corticosteroids are classified into five groups: A, B, C, D1, and D2. Substances from the same group are thought to cross-react, but a patient sensitized to one or a group of glucocorticoids does not have to avoid all types of glucocorticoids. Challenge testing is the best way to select alternatives that are safe[1,9]. In this case, the patient was sensitized to group A corticosteroids but tolerated budesonide and dexamethasone.

Rapid recognition and appropriate management of anaphylaxis are crucial to prevent potentially fatal outcomes, and accurate identification of the causative agent is pivotal to prevent subsequent exposure.

It is important to stay vigilant when prescribing medication, even in patients with no prior history of adverse reactions. The potential for idiosyncratic responses to any medication, including those considered relatively safe, must be acknowledged and carefully evaluated.

In conclusion, this case report highlights the importance of recognizing anaphylaxis induced by glucocorticoids and aims to contribute to the growing body of literature on immediate hypersensitivity reactions to glucocorticoids.

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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

A new disorder to keep in mind: VEXAS syndrome

Uma nova entidade a ter em consideração: síndrome VEXAS

Egídio Freitas[1], Miguel Nogueira[1], Ana M. Lé[1], André Coelho[2], and Inês Lobo[1]*

[1]Department of Dermatology; [2]Department of Pathological Anatomy. Centro Hospitalar Universitário de Santo António, Porto, Portugal

Abstract

The VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), which has recently been described, is a monogenic autoinflammatory syndrome that primarily affects males and has its onset in adulthood. The disease is caused by somatic mutations in the *UBA1* gene (*ubiquitin-like modifier activating enzyme 1*), which is responsible for cellular processes, particularly in maintaining protein homeostasis. It presents with severe and progressive systemic inflammation that is resistant to therapy. Common symptoms include fever and constitutional syndrome, along with hematological manifestations such as macrocytic anemia, other cytopenias, myelodysplastic syndrome, and characteristic vacuolization of myeloid and erythroid cells. Additional symptoms may involve the skin (neutrophilic dermatosis), lungs, chondritis, and vasculitis. Thus, in a case where a male patient presents with recurrent neutrophilic dermatosis unresponsive to treatment, macrocytic anemia, and systemic autoinflammatory manifestations, it is important to suspect this newly identified condition and proceed with a confirmatory genetic test.

Keywords: VEXAS syndrome. *UBA1* gene. Neutrophilic dermatosis.

Resumo

A síndrome VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), recentemente descrita, consiste numa síndrome autoinflamatória monogénica de início na idade adulta que afecta quase exclusivamente o sexo masculino. A doença é causada por mutações somáticas no gene *UBA1* (*ubiquitin-like modifier activating enzyme 1*), responsável por processos celulares, principalmente pela manutenção da homeostase proteica. Manifesta-se com inflamação sistémica, muitas vezes grave, progressiva e refractária à terapêutica. Cursa frequentemente com febre e síndrome constitucional associada a alterações hematológicas (anemia macrocítica e outras citopenias, além de síndrome mielodisplásico e vacuolização característica de células mielóides e eritróides), cutâneas (dermatose neutrofílica), pulmonares, condrite e vasculite. Deste modo, e qual como se verificou neste caso, na presença de um doente do sexo masculino, com dermatose neutrofilica recidivante e refratária ao tratamento, anemia macrocitica e com manifestações autoinflamatórias e sistémicas, devemos suspeitar desta nova entidade e realizar o teste genético confirmatório.

Palavras-chave: Síndrome VEXAS. Gene *UBA1.* Dermatose neutrofílica.

***Correspondence:**
Egídio Freitas
E-mail: egidiofreitas68980@gmail.com

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Introduction

In the year 2020, Beck et al. introduced a groundbreaking autoinflammatory syndrome known as VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic)[1]. This syndrome represents a recent discovery that has forged connections between previously unrelated inflammatory disorders and serves as an exemplar for a new class of hemato-inflammatory diseases[2]. VEXAS syndrome is an acknowledged monogenic autoinflammatory disorder that predominantly emerges in adulthood, typically in the fifth decade of life or later, and demonstrates a marked male predominance[3].

While the precise prevalence of VEXAS syndrome remains uncertain, it is noteworthy that more than 200 cases have been documented in the medical literature, suggesting that it may be more prevalent than originally believed[2]. This condition is characterized by somatic mutations in the X-chromosomal *UBA1* gene, which plays a pivotal role in maintaining protein homeostasis within hematopoietic progenitor cells[1]. It is marked by profound and relentless systemic inflammation, often presenting as a severe and progressively deteriorating clinical condition that is unresponsive to conventional therapeutic modalities (namely methotrexate, mycophenolate mofetil, and azathioprine)[2].

The clinical manifestations of VEXAS syndrome can vary, with systemic inflammation predominantly impacting the skin, lungs, blood vessels, and cartilage. Key clinical features encompass the presence of fever, the presence of vacuoles in neutrophilic and erythroid precursors, elevated inflammatory markers, and cytopenias[3]. Dysplastic changes in the bone marrow may manifest as macrocytic anemia and thrombocytopenia and could eventually progress to a myelodysplastic syndrome[3]. Cutaneous symptoms typically present as Sweet-like multiple, firm, tender, infiltrated erythematous or violaceous papules, nodules, and plaques affecting the trunk, limbs, and neck. Notably, cutaneous signs are part of the initial presentation in approximately 63% of patients. Dermatologists frequently assume a pivotal role in the diagnostic process of VEXAS syndrome, given that cutaneous manifestations can serve as indicators of potential systemic complications[2]. The relentless inflammation observed in VEXAS syndrome leads to symptoms such as fever, fatigue, weight loss, lymphadenopathy, pulmonary infiltrates with neutrophilic alveolitis, pulmonary vasculitis, venous thromboembolism, inflammatory arthritis, synovitis, serositis, as well as ophthalmic complications such as uveitis and scleritis. Disease-related mortality varies between 40 and 63% in different case series, consistently reflecting high mortality rates with substantial associated morbidity[1].

The objective of this article is to present a case of VEXAS syndrome with the aim of increasing awareness about this recently identified medical condition.

Clinical case

We describe the case of a 78-year-old man, with a personal medical history of type 2 diabetes mellitus, hypertension, and dyslipidemia. He had no significant family medical history and reported no allergies to medications. At the age of 72, he presented with a 2-month history of pruritic, erythematous-violaceous, tumescent, annular plaques on his face, back, and limbs (Fig. 1). There was no recent history of medication use, and systemic symptoms were absent. The initial diagnostic considerations included Sweet syndrome, urticarial vasculitis, cutaneous lymphoma, and lupus tumidus. Consequently, a skin biopsy was performed for histopathological examination (HE staining). The skin biopsy revealed a dermal papilla edema and a perivascular and interstitial dermal inflammatory infiltrate primarily composed of neutrophils, characterized by intense karyorrhexis (leukocytoclasia) with the participation of occasional lymphocytes and xanthomatous macrophages (Fig. 2). Further investigations were conducted, including a complete blood count, peripheral blood smear, age-appropriate oncological screening, serological evaluations, Interferon Gamma Release Assay, blood and urine protein electrophoresis, antinuclear antibodies (ANA) testing, anti-SS-A and anti-SS-B antibodies, rheumatoid factor assessment, complement studies, and peripheral blood cytometry. These investigations did not reveal clinically significant abnormalities. The patient was treated with prednisolone 1 g/kg/day, followed by hydroxychloroquine 400 mg/day, dapsone 100 mg/day, and salazopyrin up to 2 g/day, sequentially with primary and/or secondary failure. Given the recurrent and refractory nature of the dermatosis, repeat skin biopsy for histopathological examination and flow cytometry were performed, yielding results consistent with the initial biopsy. At 74 years of age, the patient concurrently developed bilateral panuveitis, which demonstrated improvement with corticosteroid therapy. Subsequently, a progressive constitutional syndrome emerged, associated with monoclonal gammopathy of uncertain significance (characterized by an IgM/kappa monoclonal protein

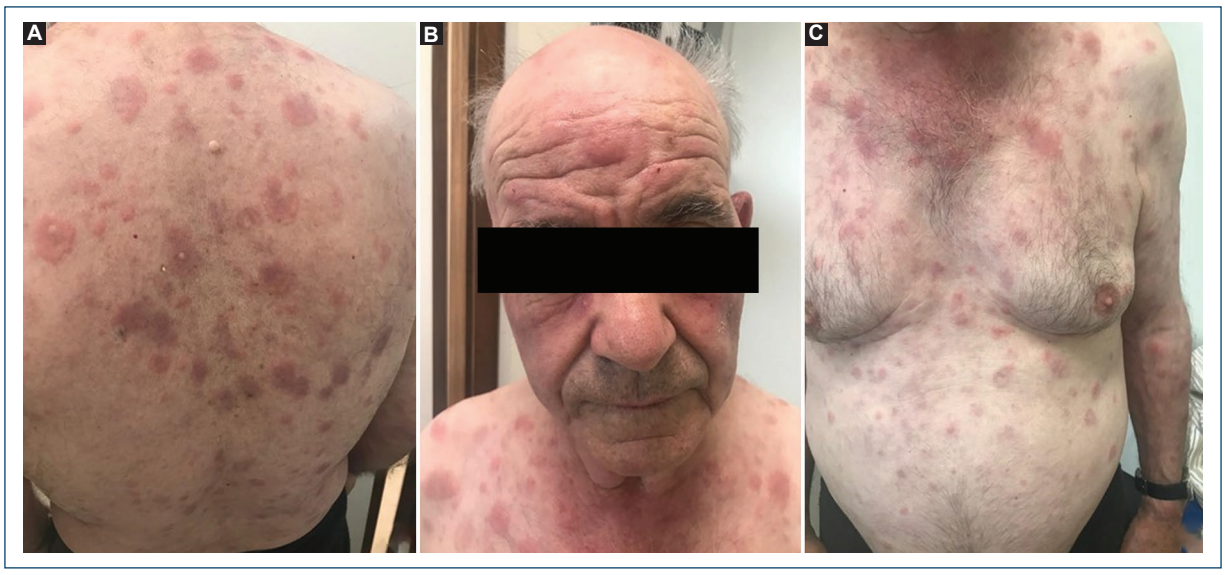

Figure 1. A-C: annular, tumid, pruritic erythematous-violaceous plaques, some arcuate on the face, back and limbs.

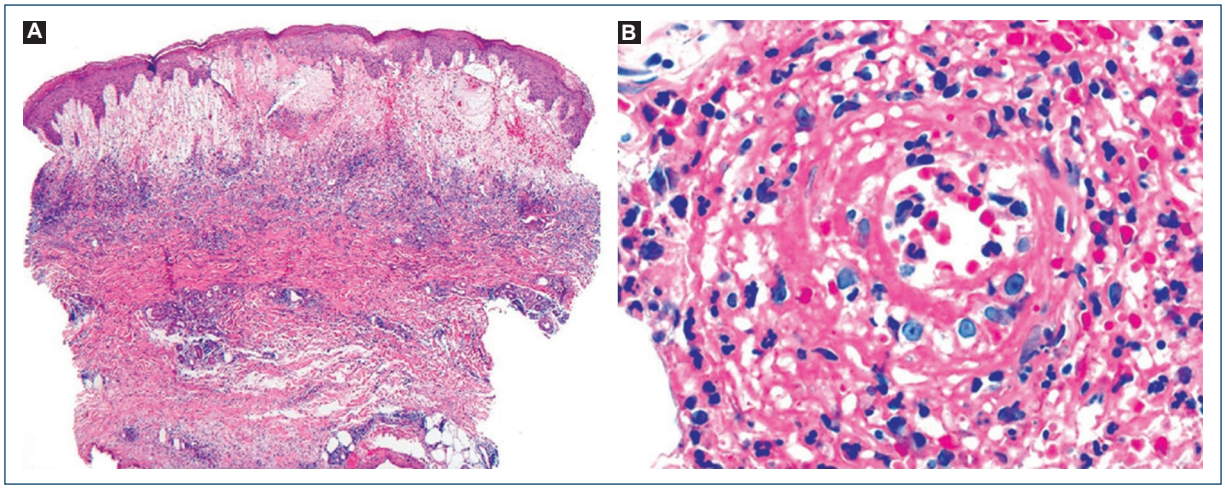

Figure 2. A and B: dermis with perivascular and interstitial inflammatory infiltrate, made up of neutrophils, with intense karyorrhexis (leukocytoclasia) and with the participation of occasional lymphocytes and xanthomatous macrophages.

peak) and macrocytic anemia. Myelogram revealed evidence of myelodysplasia. Thoracic, abdominal, and pelvic computed tomography revealed no pertinent clinical alterations. Considering these clinical and laboratory findings, the patient's advanced age, and his male gender, the possibility of VEXAS syndrome was entertained. Peripheral blood genetic testing involving direct sequencing of exon 3 of the UBA1 gene conclusively verified somatic mosaicism within the gene, elucidating the presence of the Met41Leu (c.121A > C) variant and, consequently, confirming the diagnosis. Therapeutic intervention included systemic corticosteroid therapy and methotrexate, which elicited a partial response. However, the patient succumbed to sepsis with a respiratory onset.

Discussion

The identification of a potential shared genetic basis for inflammatory skin conditions offers valuable insights into the underlying mechanisms governing cutaneous inflammation[2].

In nearly all individuals diagnosed with VEXAS syndrome, specific missense mutations have been pinpointed at codon 41 of the *UBA1* gene, with the following frequencies: p.Met41Thr (c.122T > C), p.Met41Val (c.121A > G), and p.Met41Leu (c.121A > C), as observed in our patient[4,5]. The *UBA1* gene encodes the *ubiquitin-like modifier activating enzyme 1*, a pivotal enzyme critical for cellular ubiquitylation. Ubiquitylation plays a crucial role in various cellular processes, including the regulation of the cell cycle, the response to DNA damage, and immune signaling pathways. Mutations in *UBA1* result in diminished ubiquitination and activation of autoimmune pathways, leading to inflammatory manifestations[5]. These mutations result in reduced expression of the cytoplasmic UBA1b isoform and the formation of the catalytically impaired UBA1c isoform[6]. Although the p.Met41Leu mutation is associated with a more favorable prognosis, indicating higher residual UBA1b expression, our patient ultimately succumbed to disease-related complications[6]. Furthermore, it has been demonstrated that different genetic variants are linked to distinct clinical presentations. Patients with the Leu variant are more likely to be diagnosed with Sweet syndrome (as observed in our case), while patients with the Thr variants are more predisposed to developing inflammatory ocular diseases, and those with the Val variant are less likely to develop ear chondritis[6].

Concerning cutaneous manifestations, these are frequently observed, with reports in up to 88% of patients, contingent on the patient cohorts[4]. The most prevalent cutaneous presentations may be non-vasculitic, including Sweet syndrome, neutrophilic dermatosis, erythema nodosum, urticaria, pressure plaques, injection site reactions, and others, or vasculitic, such as leukocytoclastic vasculitis[3].

The *UBA1* mutation was identified within skin tissues through genetic sequencing and analysis of samples obtained from VEXAS patients, mirroring the genetic anomalies seen in myeloid cells[7]. Consequently, it is theorized that the infiltration of dermal tissue arises from the clonal expansion of *UBA1* mutant cells, rather than originating from an inflammatory context. In contrast, a separate study found that *UBA1* mutations were exclusively detected in skin tissues of patients suffering from neutrophilic dermatosis and were notably absent in other dermatological conditions, such as leukocytoclastic cutaneous vasculitis[8]. This observation raises the possibility that *UBA1* mutant clones may be absent in non-neutrophilic dermatitis or exist in quantities too small to be reliably detected. This disparity gives rise to different therapeutic strategies, either directed at targeting the *UBA1* mutation or at ameliorating the inflammatory response[3].

Given the systemic nature of VEXAS syndrome and its potential effects on multiple organ systems, including the lungs, blood vessels, and potentially the bone marrow, the application of computed tomography (CT) scanning arises as a valuable diagnostic tool. A CT scan provides detailed information regarding the extent of systemic involvement, especially in the thoracic region, which holds relevance for both precise diagnosis and the development of treatment strategies. This significance is emphasized by the patient's pulmonary symptoms and the heightened incidence of pulmonary involvement observed in VEXAS syndrome[3].

Patients may initially seek dermatological care for skin lesions, emphasizing the importance for dermatologists to consider VEXAS syndrome in their list of potential differential diagnoses. VEXAS syndrome should be contemplated in adult men exhibiting systemic symptoms, such as fever and fatigue, and presenting with sensitive, purpuric, or erythematous infiltrated nodules, periorbital edema, chondritis, or refractory vasculitis. Suspicion should be heightened if an abnormal blood count with cytopenias, elevated inflammatory markers, and a biopsy supporting neutrophilic dermatosis, with or without leukocytoclastic vasculitis, is present[2]. These patients should be referred for potential bone marrow examination to check for characteristic vacuoles in neutrophilic and erythroid precursors or for a definitive diagnosis through genetic sequencing.

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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.

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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

Imported tungiasis: case report

Tungíase importada: relato de caso

Rafael Mira, Ana L. Magalhães, Ana C. Esteves, and Miguel S. Sobrado*

USF Lavradio, ACES Arco Ribeirinho, Barreiro, Portugal

Abstract

Tungiasis is a skin parasitosis caused by a flea. It is very prevalent in underdeveloped countries and rare in developed countries, particularly in Europe. The disease is acquired through direct contact with infected soil, mainly on the feet after the host has been barefoot. The disease is typically self-limited and its diagnosis is essentially clinical due to its typical clinical presentation. This report presents a case of imported tungiasis in Portugal, in a 21-year-old male patient after returning from a vacation in a country with a high prevalence of this parasite. The patient had three typical tungiasis lesions, with no associated complications. The parasites were surgically excised without complications. The aim of this report is to contribute to knowledge of this pathology, which is largely unknown to the majority of the medical community. Its identification is essential due to the increase in globalization, tourism, and the importation of this pathology.

Keywords: Tungiasis. Skin disease. Sand flea. *Tunga penetrans*. Case report.

Resumo

A tungíase é uma parasitose cutânea causada por uma pulga, sendo prevalente em países subdesenvolvidos, sendo rara a sua apresentação em países desenvolvidos, nomeadamente na Europa. A doença é adquirida através contacto direto com o solo infetado, sendo adquirida principalmente nos pés após o hospedeiro ter andado descalço. A doença é tipicamente autolimitada e o seu diagnóstico é essencialmente clínico devido à sua apresentação clínica típica. Neste relato apresenta-se um caso de importação de tungíase em Portugal num utente masculino de 21 anos após regressar de férias num país com alta prevalência deste parasita. O utente apresentava três lesões típicas de tungíase, sem complicações associadas. Foi realizada a excisão cirúrgica dos parasitas sem intercorrências. Com este relato pretende-se contribuir para o conhecimento desta patologia muito desconhecida pela maioria da comunidade médica, sendo essencial a sua identificação devido ao aumento da globalização, do turismo e da importação desta patologia.

Palavras-chave: Tungíase. Doença cutânea. Pulga da areia. *Tunga penetrans*. Relato de caso.

***Correspondence:**
Rafael Mira
E-mail: rafael.vitoria.mira@gmail.com

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Introduction

Tungiasis is a parasitic skin infection caused by the female sand flea *Tunga penetrans*, when it comes into contact with the skin and penetrates it[1]. This parasitosis is endemic to tropical and subtropical areas, typically in underdeveloped countries[2]. This disease is known by various names across the globe: *chigoe*, *jigger*, *sand flea*, *puce-chique*, *kuti*, *suthi pique*, *níguas*, *bicho do pé* or *pulga de bicho*[3]. Although it is not present in Europe, it is possible to observe this pathology in tourists, especially those staying in more rural areas and in local accommodations[4].

The following case has the purpose to illustrate a disease that is not so well known in the European medical community but that needs better recognition due to globalization, easy access to travel, and close relations with certain communities[3,4].

Clinical case

A 21-year-old man, caucasian, living in Portugal, with no previous medical or surgical history, no medication, and no documented allergies, with an up-to-date vaccination plan, was observed in the acute illness consultation at his primary health-care center with three pruritic skin lesions on his toes beginning the previous week, with a foreign body sensation and discomfort when walking, but no pain or any other symptoms or previous injuries. The patient reported having spent 2 weeks on vacation in Brazil, in a rural area, having been barefoot on the beach and the land near his accommodation.

Inspection revealed three firms isolated 5 mm papules, bright yellow with a black central region, on the 1st and 4th toes of the left foot and the infra-ungual region of the 3rd toe of the right foot (Figs. 1-3). Lesions showed no signs of surrounding inflammation and no other lesions could be observed.

Based on the description of the lesions, symptoms, and recent trip to Brazil, the first diagnostic hypothesis was tungiasis. The patient was referred to the emergency department of the nearest hospital where the three parasites were extracted and the locae were debrided. Within 2 weeks, there was a complete recovery.

Discussion

Tungiasis is a parasitic disease endemic to tropical and subtropical areas, typically found in underdeveloped countries, particularly in sub-Saharan Africa,

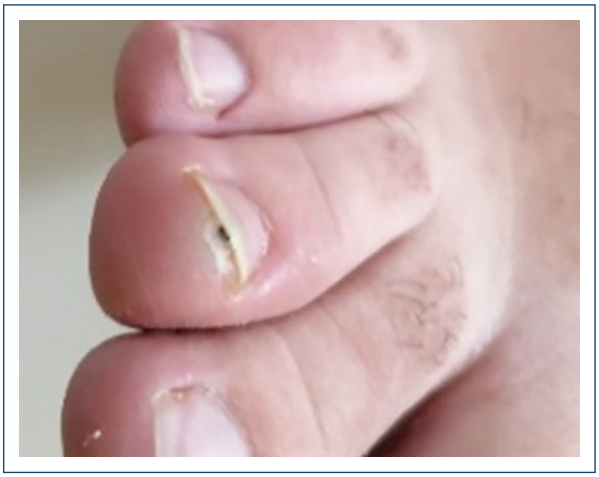

Figure 1. Infra-ungual tungiasis lesion, 3rd toe of the left foot.

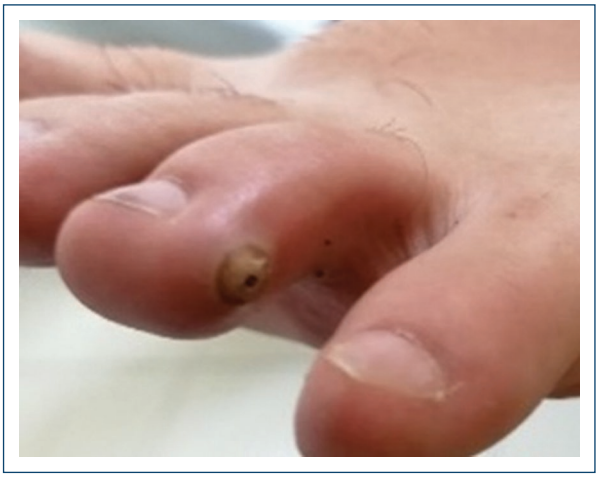

Figure 2. Tungiasis lesion on the external lateral surface of the 4th toe of the right foot.

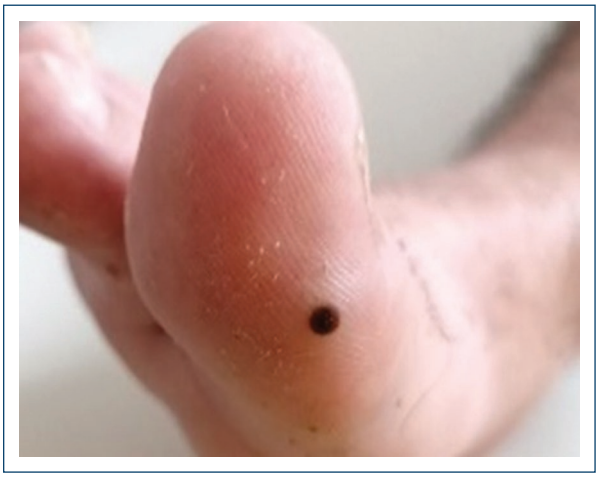

Figure 3. Tungiasis lesion on the external surface of the 1st toe of the right foot.

South America, and the Caribbean[2,5]. This parasitosis is more prevalent in more populated places, with poor sanitary and housing conditions and with reservoir animals present (rats, cats, cows, pigs, and dogs)[6-8]. The parasite is found in sandy soil and beach sand and is transmitted through direct contact.

The parasite begins its life cycle after hatching from an egg in the form of a larva that feeds on organic compounds in the environment. After growing, the larva pupates and becomes an adult flea. The adult male and female fleas feed intermittently on the blood of their hosts, but only the pregnant female flea is able to penetrate the host, which is essential for the parasite's life cycle. The pregnant flea penetrates the skin through its cephalic portion, leaving the terminal portion in contact with the outside that allows the flea to breathe and expel feces and white eggs, and gives the skin lesions a black color in the center that contributes to the clinical identification. After 5-6 weeks, the flea dies and is expelled by the host after several weeks[9,10].

Tungiasis differs in terms of epidemiology, clinical presentation, and complications between tourists and inhabitants of endemic regions: in tourists, the disease is typically benign and self-limited, whereas in endemic areas, the disease can be very disabling due to the longer exposure time and number of parasites[2]. In tourists, due to the penetration of isolated fleas, the disease usually presents as isolated papular or nodular lesions with white, gray, or yellowish color, surrounded by hyperkeratosis, and a small brown-to-black central opening, sometimes with eggs on the adjacent skin, corresponding to the posterior portions of the abdomen of the flea[4,11]. The lesions may be associated with itching, pain, skin desquamation, and foreign body sensation[6,8]. Typically, lesions occur on the feet (due to walking barefoot), typically on the toes, the interdigital region, and the infra-ungual region, but lesions may also be present on other parts of the body, such as the hands or back, if the person sleeps on the floor. In individuals living in endemic countries or in immunocompromised patients, lesions can be found in aggregate forms with up to 30 parasites in the same area, causing deformation of the adjacent skin, more often with hyperkeratosis, deformation of the extremities, bacterial over-infection, and gangrene[1,2,4,7,9]. In addition, other less common clinical presentations have been described, such as plantar wart-like lesions, crusted, bullous, pustular, and ulcerative lesions[11].

The diagnosis of tungiasis is made clinically, based on the presence of typical lesions together with a corresponding travel history to an area where tungiasis is endemic[11]. Dermatoscopy has been shown to be helpful to aid the diagnosis of tungiasis, particularly in non-endemic regions[4,6,11,12]. The classical characteristics are a brown-to-black central pore, a white halo corresponding to the enlarged abdomen of the parasite, and a peripheral bluish-gray area corresponding to the parasite exoskeleton[4]. Confirmation of the diagnosis is made with microscopic analysis, which shows hyperkeratosis, parakeratosis, and acanthosis[2,11]. The flea is localized in the upper dermis, surrounded by a pseudo-cystic cavity. Eggs are also observed inside the flea. A perilesional, inflammatory infiltrate, is also present[11].

The differential diagnosis of tungiasis may include viral warts, cutaneous myiasis, granuloma of foreign bodies, arthropod bites, ingrown foot nails, bacterial infections, pyogenic granuloma, malign tumors (melanoma and squamous cell carcinoma), and myxoid cysts[3,4,5,6,9,11].

Treatment of choice is complete surgical excision of the parasite, with subsequent disinfection of the site[2,4,9]. Antibiotic therapy is not necessary unless there are signs of bacterial over-infection[2,4]. Vaccination status against tetanus should be checked and updated and prophylaxis may be necessary[2,3,4,11]. However, the surgical option is not recommended in severe infections with the presence of several parasites. There is still no topical or oral treatment with satisfactory results for tungiasis, but some studies report on the use of ivermectin and thiabendazole, especially topical[2,9,10,11].

Prevention consists mainly of avoiding contact with contaminated soil, wearing closed shoes when in contact with soil and sand, and regular inspection of the feet for early identification of skin lesions[4,10]. In addition, some studies indicate the use of a plant-based repellent Zanzarin® (made up of coconut oil, jojoba oil, and aloe vera) to reduce the number of lesions[2,9,10,13]. Regular decontamination, implementation and improvement of sanitary measures, and the removal of parasite reservoir animals can reduce prevalence.

We present this case to emphasize the existence of this tropical disease, which is not so well known in the medical community in non-endemic countries[14], but whose recognition is important, given the increase in globalization, tourism, and social migration phenomena.

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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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Use of artificial intelligence to generate texts. The authors declare that they did not use any type of generative artificial intelligence in writing this manuscript, nor to create figures, graphs, tables, and/or their respective captions.

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DERMATOLOGY IMAGES

Do not forget to consider eosinophilic ulcer of the tongue!

Não se esqueça de considerar a úlcera eosinofílica da língua!

Miguel Santos-Coelho, Joana A. Barbosa, and Alexandre João*

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

An 81-year-old, non-smoker woman presented with slowly growing and mildly painful tongue ulcers that had been first noted 3 months earlier.

Clinical examination revealed three ulcers of the tongue's body, measuring between 0.4 and 1 cm, with a gray base and irregular, defined, slightly infiltrated borders (Fig. 1). There were no palpable lymph nodes and no teeth abnormalities.

Polymerase chain reaction testing for herpes simplex virus (HSV) and treponema pallidum hemagglutination, venereal disease research laboratory, and human immunodeficiency virus (HIV) serologies were negative. A punch biopsy revealed ulceration, densification of collagen, vascular proliferation, and a mixed inflammatory infiltrate with lymphocytes, histiocytes, and eosinophils that extended through the striated muscle fibers (Fig. 2). A diagnosis of eosinophilic ulcer of the tongue (EUT) was made.

After discussing possible treatments, a wait-and-see approach using topical lidocaine for pain management was selected. Lesion resolution occurred 4 months later, with no recurrence at 12-month follow-up.

EUT is a benign, self-limited entity, usually diagnosed during the 1st year or between the 5th and 7th decades of life[1-4]. Most lesions are solitary, asymptomatic, and located on the tongue[1-4]. Local trauma (biting, deformed teeth) is one of the drivers for EUT[1-4] but is insufficient to explain lesion progression.

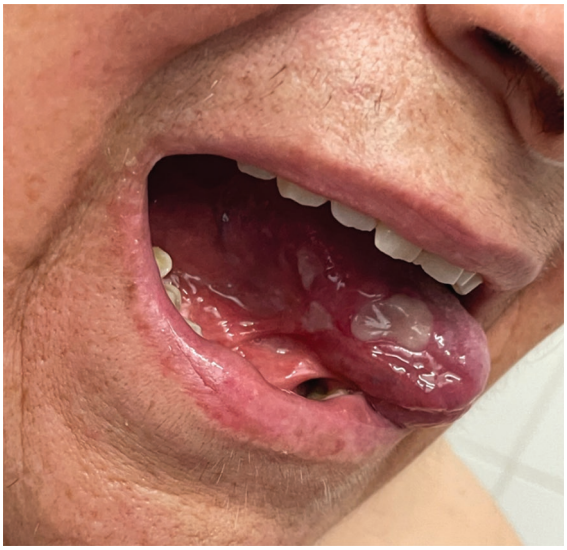

Figure 1. Ulcers of the tongue's body.

Differential diagnosis includes inflammatory (aphthous stomatitis and oral lichen planus), autoimmune

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

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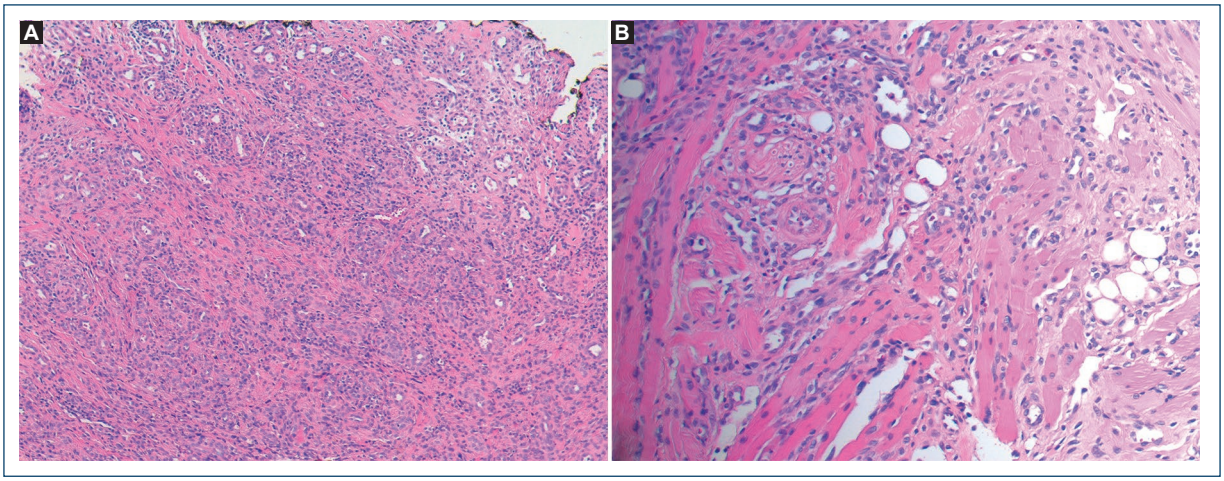

Figure 2. A: punch biopsy revealing ulceration, collagen densification, and a dense mixed infiltrate containing eosinophils (H&E, ×100); **B:** vascular proliferation and inflammatory infiltrate extending through striated muscle fibers (H&E, ×200).

(Behçet, pemphigus vulgaris, and systemic lupus erythematosus), infectious (HSV, syphilis, HIV), and malignant (squamous cell carcinoma) diseases.

A wait-and-see approach can be used and surgical excision, cryosurgery, and topical/intralesional corticosteroids are options for persistent lesions[1-4]. Recurrence is rare but removal of possible triggers (behavioral modification, dental care) is also important.

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Conflicts of interest

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Ethical disclosures

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

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

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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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DERMATOLOGY IMAGES

Disseminated cutaneous leishmaniasis due to *Leishmania guyanensis* in an infant

Leishmaniose cutânea disseminada por *Leishmania guyanensis* em recém-nascido

Isabella C. Mendes-Alexandre[1], Antônio P. Mendes-Schettini[2], Felipe J. de Araújo-Santos[3], Gabriel P. Seabra-Nunes[4], Gabriela Evangelista-de Almeida[5], Jorge A. de Oliveira-Guerra[6], Matheus Alecrim-Alexandre[7], Rosilene Viana-de Andrade[8], and Luciana Mendes-dos Santos[9]*

[1]Division of Dermatology, Hospital Universitário Getúlio Vargas, Manaus; [2]Department of Pathology, Fundação Alfredo da Matta (FUAM), Manaus; [3]Department of Mollecular Biology, Fundação Alfredo da Matta (FUAM), Manaus; [4]Division of Internal Medicine, Instituto de Assistência Médica ao Servidor Público do Estado (IAMSPE), São Paulo; [5]Division of Dermatology, Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD), Manaus; [6]Division of Leishmaniasis and Infectology, Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD), Manaus; [7]Division of General Surgery, Hospital SAMEL, Manaus; [8]Department of Pathology, Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD), Manaus; [9]Department of Dermatology, Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD), Manaus. Brazil

A 5-month-old male toddler from Óbidos, Brazil, presented progressive erythematous-brown plaques and papules on the face and limbs since he was 2 weeks old (Figs. 1A, B and C). Leishmania amastigote was confirmed through a skin biopsy (Fig. 2), being confirmed *Leishmania Viannia guyanensis* in DNA amplification technique using polymerase chain reaction.

Initial treatment with intravenous pentavalent antimonial 1 mg/kg/day caused fever and tonic-clonic seizures, leading to a switch to pentamidine 4 mg/kg intramuscularly once a week for 3 weeks. The patient showed satisfactory resolution of symptoms 1 week after the last dose of pentamidine. The skin lesions evolved as definitive atrophic scars after the treatment (Fig. 3A, B and C).

Cutaneous leishmaniasis (CL) has diverse clinical presentations and can be challenging when the clinical presentation is different from the classic ulcerated form[1]. In the neonatal period, CL often mimics other conditions, such as histiocytosis, lymphomas, and syphilis[2,3]. CL commonly affects children aged 2-12 years, corresponding to 10% of cases in endemic areas[2,4].

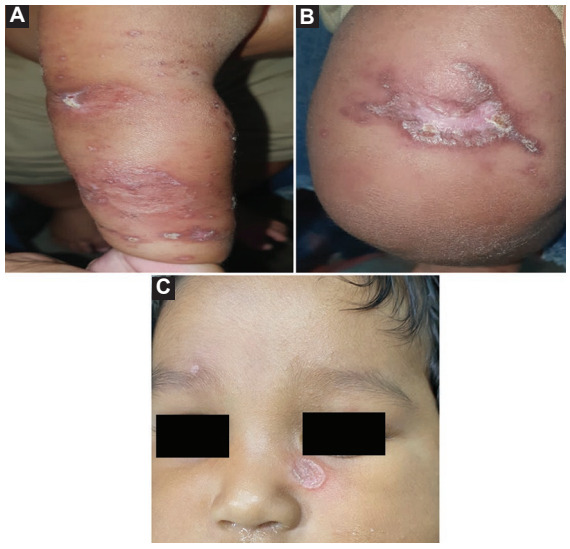

Figure 1. Lesions observed in the first outpatient visit. **A:** erythematous violaceous ulcerative plaques with crusts on the right arm. **B:** infiltrated and ulcerated plaque with erythematous violaceous edges on the left thigh. **C:** erythematous framed ulcerated lesion on the malar region.

***Correspondence:**
Isabella Mendes-Alexandre
E-mail: bellac_mendes@hotmail.com

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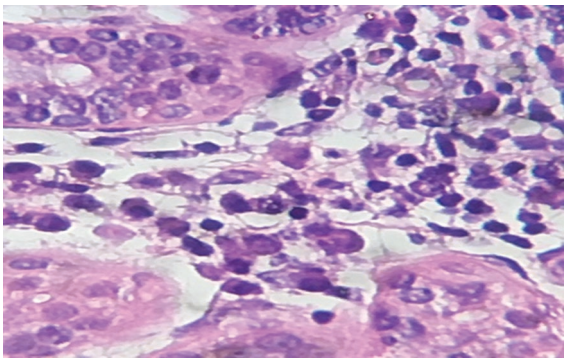

Figure 2. Histopathology from a skin lesion on the right arm demonstrating vacuolated histiocytes containing amastigotes of leishmania inside (H&E 100×).

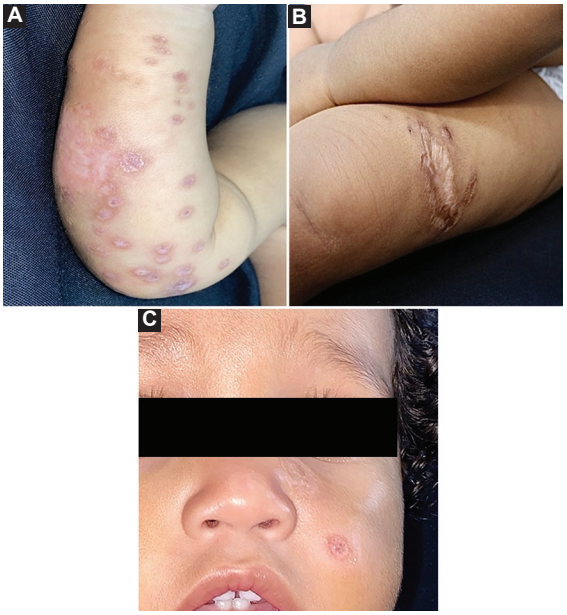

Figure 3. A-C: satisfactory response after completing treatment with three doses of pentamidine.

Treatment of pediatric CL has higher rates of therapeutic failure compared to adults, depending on differences in the immune response and medication tolerance that contribute to this disparity[4]. In addition, children have poor tolerance to systemic medications, which may be common and potentially serious adverse events[4,5].

Combination therapies, such as paromomycin, imiquimod, and amphotericin B, are being studied for optimal outcomes and reduced side effects[5]. The use of pentamidine for *L. guyanensis* infections is recommended, although off-label for children under 2 years old.

Although the reported case showed positive response and tolerability to pentamidine, further research is needed to improve CL treatment and minimize complications, aiming to reduce deformities and risks for affected patients.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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DERMATOLOGY IMAGES

Following the path: an unusual location for cutaneous larva migrans

Seguindo o caminho: uma localização incomum para larva migrans cutânea

Miguel Santos-Coelho, Joana A. Barbosa, and Juliana Baptista*

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

A 28-year-old woman with no relevant past medical history presented to the Dermatology department with pruriginous, slowly growing lesions on her right abdominal flank. The lesions had been first noted a week earlier, after returning home from a trip to Mexico. She denied other symptoms.

Clinical examination revealed several erythematous papules and plaques with a serpiginous distribution affecting the right abdominal flank (Fig. 1). The remaining physical examination was unremarkable. Based on clinical presentation and considering the recent travel history, a diagnosis of cutaneous larva migrans was made.

The patient was treated with single dose oral ivermectin (200 mcg/kg), with full resolution of lesions at 1-month follow-up.

Cutaneous larva migrans is an infection caused, most frequently, by *Ancylostoma braziliense* (a hookworm transmitted by soil contaminated with feces of cats or dogs)[1,2]. Although worldwide distributed (and with some reported autochthonous cases in Europe[3]), infections are more frequently found in tropical/subtropical countries in Central and South America and Asia[1].

After penetrating the skin, the larva undergoes epidermal migration, giving rise to the characteristic clinical appearance. The lower limbs (especially the feet) are the most common locations for lesions, but the trunk, as in our patient, can be affected in up to 7% of cases[4]. Exceptionally, hematogenous dissemination to the lungs can occur[4].

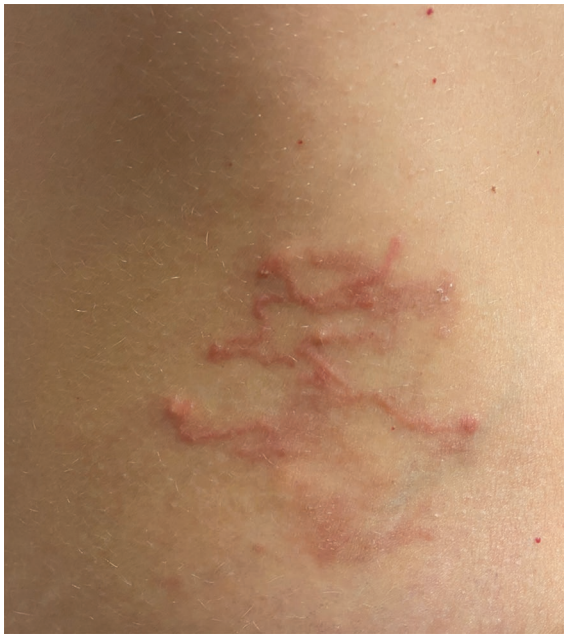

Figure 1. Lesions of the right abdominal flank.

Although self-limited, treatment with oral albendazole or ivermectin relieves pruritus and decreases the chance of bacterial superinfection[1]. In cases where oral

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

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therapy is not possible, patients can be treated with topical treatment using ivermectin 1% or thiabendazole 15% cream[3,5].

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Conflicts of interest

None.

Ethical disclosure

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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