ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Erythema multiforme: diagnosis and treatment

Eritema multiforme: diagnóstico e tratamento

Sónia Pereira Garcia[1], Cristina Valente[1], Joana Barradas Lopes[1], Cátia Santa[1], Inês Lopes[1], Isabel Rosmaninho[1]

ABSTRACT

The recognition and adequate treatment of erythema multiforme (EM) are challenging. In this review, we summarize the main aspects of the etiology, diagnosis, and treatment of EM. EM is an acute self-limited immune-mediated disease characterized by typically erythematous target lesions on the skin, although the mucous membranes may also be affected. It occurs predominantly in young female adults. The etiology varies, but the main causative agent is herpes simplex virus (HSV). Diagnosis is clinical, based on medical history and through skin examination. A skin biopsy may be performed in cases of doubtful diagnosis, and an analytical study may show nonspecific changes. Urticaria appears as a differential diagnosis in EM. This review addresses two clinical cases referred from primary care to the immunoallergology department. In acute episodes of EM, management is based on removal or treatment of the causative factor. Most episodes resolve spontaneously within a few weeks. However, in some cases, treatment for symptom relief may be necessary using oral antihistamines or topical and systemic corticosteroids in more severe cases. When HSV is identified as the causative factor in multiple EM recurrences, antiviral prophylaxis is indicated.

Keywords: Erythema multiforme, herpes simplex, diagnosis, differential diagnosis.

RESUMO

O reconhecimento e tratamento adequado do Eritema Multiforme (EM) é um desafio. Nesta revisão, sumarizam-se os principais aspectos da etiologia, diagnóstico e tratamento do EM. O EM é uma doença imunomediada aguda e autolimitada, caracterizada por lesões cutâneas eritematosas tipicamente em forma de alvo, podendo as mucosas estar também afetadas. O EM acomete maioritariamente adultos jovens, do gênero feminino. A sua etiologia é variada, sendo o principal agente causal o Vírus Herpes Simplex (VHS). O diagnóstico de EM é clínico, baseado numa história clínica e exame objetivo cutâneo pormenorizado. A biópsia cutânea poderá ser realizada em caso de dúvidas no diagnóstico e o estudo analítico poderá apresentar alterações inespecíficas. A urticária surge como diagnóstico diferencial mais comum no EM. Nesta revisão abordam-se dois casos clínicos enviados pelos cuidados primários à consulta de Imunoalergologia. Quando perante um episódio agudo de EM, o tratamento consiste na remoção ou tratamento do fator causal. A maioria dos episódios resolve-se espontaneamente em poucas semanas. Todavia, em alguns casos, poderá ser necessário tratamento de alívio sintomático, nomeadamente, anti-histamínicos orais e corticoides tópicos ou sistêmicos nos casos mais graves. Quando o VHS é identificado como fator causal das várias recorrências de EM está indicada a profilaxia antiviral.

Descritores: Eritema multiforme, herpes simples, diagnóstico, diagnóstico diferencial.

Introduction

This article reviews the etiology, diagnosis, and treatment of erythema multiforme (EM), discussing two clinical cases referred by primary health care to our immunoallergology department.

EM is an acute, self-limiting, immune-mediated disease characterized by erythematous, typically target-shaped, skin lesions that affect less than 10% of the body surface area.[1] Its distribution is centripetal

1. Unidade Local de Saude de Gaia e Espinho, Departamento de Imunoalergologia, Vila Nova de Gaia, Porto, Portugal.

Submitted May 15 2024, accepted May 23 2024.

Arq Asma Alerg Imunol. 2024;8(3):263-8.

http://dx.doi.org/10.5935/2526-5393.20240040-en

and symmetrical, initially affecting the limbs and then the trunk. The lesions develop over a few days and generally resolve within 3 to 5 weeks.[2]

In some cases, the mucous membranes may be affected by ulcers and blisters, and systemic symptoms, such as fever and arthralgia, may occur, which classifies these cases as major EM. Cases that do not involve the mucous membranes or systemic symptoms are classified as minor EM.[3]

Cases involving multiple acute episodes (> 6 per year) are known as recurrent EM. Cases of persistent EM are rare and involve continuous episodes throughout the year, with widespread typically necrotic bullous papular lesions.[3]

Although EM prevalence data are limited, they indicate that it affects < 1% of the population, with the majority of cases occurring in young adults (20-40 years of age). It is slightly more predominant among women (1.5:1).[4]

Etiology

EM can be triggered by several factors. In about 90% of cases, the etiological factor is viral, bacterial, or fungal infection. The most frequent infectious agent is the herpes simplex virus (HSV), which accounts for approximately 80% of EM cases due to infection.[4] The second most common infectious agent is *Mycoplasma pneumoniae*, which mainly affects children.[5]

Drugs are the second most common etiological factor (approximately 10% of cases), the most frequent of which are non-steroidal anti-inflammatory drugs, sulfonamides, and antiepileptics.[4] In a minority of patients, EM can also be triggered by autoimmune diseases, neoplasms, or radiation.[5]

Cases with an undetermined etiological factor are called idiopathic EM, although studies have detected HSV DNA in approximately 44% of patients diagnosed with idiopathic EM.[6] According to some studies, the HLA 36 and HLA 35 phenotypes have a greater predisposition to EM.[3,4]

Pathogenesis

The mechanism by which the typical clinical manifestations of EM are triggered is thought to vary slightly depending on the precipitating factor. The pathogenesis of EM is most easily studied in cases where HSV is the triggering factor.[6] EM secondary to HSV infection appears to be due to the deposition of immune complexes, which leads to skin lesions.[4] Upon reactivation of the HSV infection, the virus is released into the bloodstream and is subsequently phagocytosed by CD34+ Langerhans cells, from which it is transferred to keratinocytes in the epidermis. The expression of HSV in epidermal cells leads to increased expression of E-cadherin in the epidermal cell membrane and the recruitment of CD4+ Th1 cells. These initiate an inflammatory cascade through the production of IFN-gamma, with lysis of infected keratinocytes and the recruitment of new T cells. These events lead to changes in the skin barrier that are characterized by visible target lesions approximately 7 to 21 days after HSV infection. In individuals with a history of HSV infection, EM does not necessarily accompany recurrent cold sores.[1,3]

Clinical manifestations

EM is characterized by target-shaped skin lesions with a central zone of necrosis, followed by two erythematous rings separated by a paler edematous zone. These lesions are usually < 3 cm and have a symmetrical acral distribution, mainly affecting the extensor surfaces of the limbs and expanding centripetally.[3] Although many of these lesions are accompanied by itching or a burning sensation, most are asymptomatic.[4]

The skin lesions appear over 3 to 5 days, lasting between 1 and 4 weeks, and may leave a residual post-inflammatory hyperpigmented papule that can persist for months.[3]

Mucous membranes may be affected, with typical lesions including erythema, erosions, and blisters.[4] Prodromal symptoms, such as fever and myalgia, rarely occur, but when they do, they precede the skin and/or mucous membrane lesions by 7 to 14 days.[3]

Diagnosis

The diagnosis of EM is clinical, based on clinical history and physical examination. In the anamnesis, it is important to ask about the onset, characteristics, location, and evolution (acute, self-limited, or episodic) of the lesions. It is important to determine the impact on daily activities and any triggering factors, namely a recent history of HSV, respiratory symptoms suggestive of *Mycoplasma pneumoniae* infection, or recent medication use. It is also important to ask about the presence of lesions in the mucous membranes.[3]

After careful anamnesis and a complete and detailed examination of the skin, it is essential to characterize the lesions and their distribution. It is important to examine all mucous membranes (oral, ocular, and genital).[7]

In cases of diagnostic uncertainty, a skin biopsy may be useful. Histological findings include the destruction of basal cells, keratinocyte necrosis, and lymphocytic infiltration around blood vessels and at the dermoepidermal junction. Papillary edema and extravasation of red blood cells may also be visible in the early stages of the lesions. In biopsies of mucosal lesions, histological evaluation is similar to that of skin lesions. Immunofluorescence microscopy findings are usually nonspecific.[4]

In the most severe cases, laboratory assessment may show an increased sedimentation rate, leukocytosis, and liver dysfunction. However, in the vast majority of cases no changes are observed.[3]

Testing for HSV antibodies in the blood may be useful if the patient is not immune, since it excludes diagnosis of EM secondary to HSV infection. If immunity to HSV is found, this indicates the possibility of, but does not confirm, HSV as a causal factor.[6]

Differential diagnosis

The target skin lesions characteristic of EM are also present in other skin pathologies, the most common of which are listed below.

– *Urticaria* is often accompanied by target lesions similar to EM, but the central area of the lesion is generally unchanged or slightly erythematous, unlike EM, in which the central portion is necrotic; however, urticaria lesions are transient, lasting < 24 hours and accompanied by intense itching, which does not occur in EM.[8,9]

– *Steven-Johnson syndrome* was formerly considered a more severe form of EM, but it has recently been considered a distinct pathology. Steven-Johnson syndrome may show more extensive epidermal necrosis, and rapid diagnosis is essential due to the possibility of life-threatening complications. Target skin lesions are macules rather than papules, which are more characteristic of EM. Furthermore, the distribution of these lesions in Steven-Johnson syndrome is centrifugal, i.e., typically more prominent on the trunk and expanding to the limbs.[10]

– *Fixed erythema* presents with lesions very similar to EM, but these lesions are fewer in number and are typically preceded by medication use. Histologically, it involves deeper extension of the inflammatory infiltrate with fewer neutrophils.[3]

– *Bullous pemphigoid* is an autoimmune pathology that, in addition to being accompanied by lesions similar to urticaria, is also accompanied by blisters. Histologically, an eosinophilic spongiotic infiltrate is visible. On closer investigation, IgG and C3 deposits are found in the basement membrane, and BP180 and BP230 antibodies are present.[3]

– *Polymorphous light eruption* is characterized by skin lesions similar to EM, although they occur after exposure to ultraviolet radiation and in exposed areas, sparing the face and back of the hands in the vast majority of cases.[3]

Treatment

For acute episodes of EM, treatment consists of removing or treating the causal factor.[1,3] However, for HSV infection, antiviral treatment does not alter the development or progression of EM.[3]

Most episodes resolve spontaneously within a few weeks. If EM lesions cause symptoms that negatively impact the patient's quality of life, symptomatic treatment is necessary. In particular, antihistamines can be used to relieve itching, topical cutaneous corticosteroids and/or oral gel can be used to reduce inflammation and accelerate the healing process, and oral antiseptics including lidocaine and diphenhydramine can be used to hinder the penetration of pathogens into mucosal lesions and reduce pain.[4]

In severe cases where topical treatment is insufficient, oral corticosteroids (prednisolone 40-60 mg/day) may be administered for 2 to 4 weeks. If there is ocular involvement, the patient must be referred to an ophthalmologist as soon as possible to assess long-term complications, namely conjunctival scarring or vision changes.[3]

For recurrent episodes of EM, the causal factor must be removed and symptom relief must be provided in acute episodes. When HSV is confirmed as the causal factor for recurrent EM, antiviral prophylaxis is indicated for 6 months to 1-2 years, depending on the response. The antiviral can be acyclovir (400 mg twice a day - 20 mg/kg/day for children), valacyclovir (500 mg twice a day), or acyclovir (250 mg twice a day). If no response occurs, these doses may be doubled. If there is still no clinical response and the symptoms have a significant impact on quality of life, other drugs may be administered, such as mycophenolate mofetil (1000-1500 mg twice a day), dapsone (100-200 mg per day), and azathioprine (100-150 mg per day).[3]

All cases can be treated on an outpatient basis, with hospitalization reserved for patients unable to

feed themselves due to extensive lesions of the oral mucosa. Mucosa lesions that can be treated on an outpatient basis must be reassessed in 2 weeks.[7]

Clinical cases

Clinical case 1

A 38-year-old woman was referred to the immunoallergology department for "recurrent urticaria with lesions on the face, knees, hands, and feet". During the consultation, the patient reported recurrent episodes, beginning in adolescence, of scattered maculopapular target-shaped skin lesions, more concentrated on the face and limbs, associated with some pruritus. The patient could not identify a triggering factor and reported that each episode lasted approximately 3 weeks, totaling approximately 3 episodes per year. After medication with antihistamines and oral corticosteroids, the symptoms improved slightly. There was no relevant information in her medical history, and she was not taking any medications regularly. The physical examination revealed maculopapular target-shaped skin lesions with a scaly center scattered across the limbs, face, and neck. The mucous membranes were

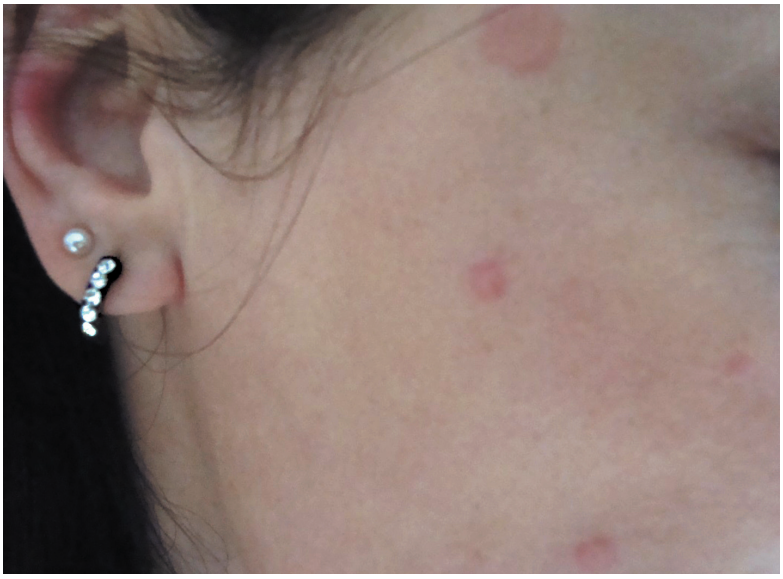

Figure 1
Target maculopapular lesions with a scaly center on the face

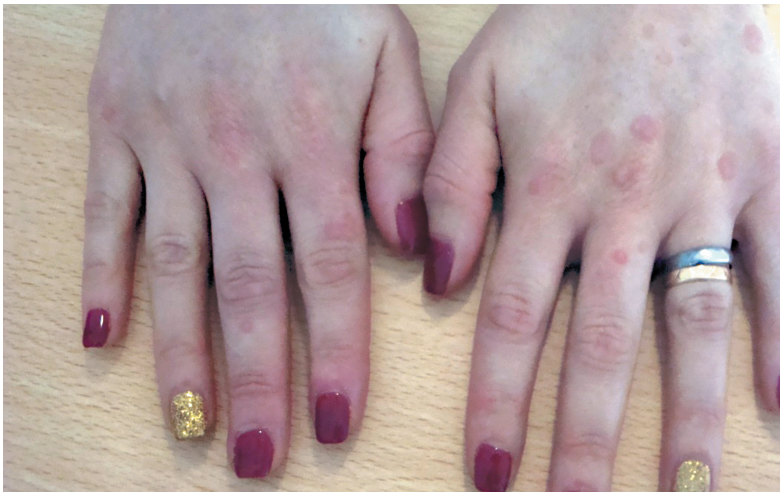

Figure 2
Target maculopapular lesions with a scaly center on the back of the hands

not affected (Figures 1 and 2). She later reported episodes of labial herpes approximately 2 weeks prior to the appearance of the skin lesions and had positive serology results for HSV type 1 IgG. Thus, she was diagnosed with EM triggered by HSV infection, and treatment with valacyclovir 500 mg twice daily was initiated. Since then, no new episodes of labial herpes or EM skin lesions have occurred, and the patient has completed 1 year of antiviral therapy.

Clinical case 2

A male adolescent was referred to the immunoallergology department due to "recurrent episodes of urticaria" for the last 3 years, with approximately 6 episodes per year. At the consultation, he reported recurrent episodes of target-shaped, pruritic maculopapular lesions that affected his face and arms, reporting heat as a possible triggering/aggravating factor. Antihistamines and oral corticosteroids had been prescribed several times and initially led to a response, but had no effect in recent episodes. He reported a significant impact on his quality of life, with school absenteeism during outbreaks that lasted approximately 1 week, although the lesions only completely resolved after 3 weeks. There was nothing significant in his medical history, and he was not taking any regular medications. Physical examination revealed numerous target-shaped skin lesions, some with a crusty center and others with violaceous centers on the face and arms, as well as lesser quantities on the legs, in addition to erythematous lesions and erosions on the labial mucosa. Other mucous membranes were not affected. He later reported episodes of labial herpes approximately 2 weeks before the appearance of the skin lesions and had positive serology results for HSV type 1 IgG. Thus, he was diagnosed with EM triggered by HSV infection, and treatment with valacyclovir (500 mg twice a day), in addition to antihistamines and oral corticosteroids, was initiated. No new episodes had occurred after 3 months.

Discussion

The cases described above were referred for an immunoallergology consultation based on a diagnosis of urticaria. In fact, urticaria can also present with maculopapular target lesions. However, these lesions are transient and migratory, generally responding well to antihistamine and corticosteroid therapy, unlike EM.

The primary etiological factor is HSV, with recurrent episodes in most cases. However, the association between HSV infection and EM is not always clear, given that cold sores are relatively common and generally not concerning to patients, not all HSV recurrences trigger EM, and there is typically a two-week interval between herpes infection and the appearance of EM lesions.

The initial treatment was symptomatic, but after determining the etiological factor and several recurrences, targeted antiviral treatment was administered, resulting in the disappearance of the lesions, with no recurrence to date.

Conclusions

EM is a self-limiting disease characterized by target-shaped skin lesions. In 90% of cases, the etiological factor is infectious, of which the most common is HSV. Its pathogenesis, although not yet fully understood, is due to the deposition of immune complexes in the skin barrier. Diagnosis is clinical and skin biopsy is rarely used.

Treatment involves removing or controlling the causative factor (HSV), which may be accompanied by corticosteroids and antihistamines for symptomatic relief. In more severe cases, immunosuppressive treatment may be necessary, but differential diagnoses must always be considered.

References

1. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on Erythema Multiforme. Clin Rev Allergy Immunol. 2018;54:177-84.
2. Zoghaib S, Kechichian E, Souaid K, Soutou B, Helou J, Tomb R. Triggers, clinical manifestations, and management of pediatric erythema multiforme: A systematic review. J Am Acad Dermatol. 2019;81:813-22.
3. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol. 2012;51:889-902.
4. Samim F, Auluck A, Zed C, Williams PM. Erythema multiforme: a review of epidemiology, pathogenesis, clinical features, and treatment. Dent Clin North Am. 2013;57:583-96.
5. Kechichian E, Ingen-Housz-Oro S, Sbidian E, Hemery F, Bernier C, Fite C, et al. A large epidemiological study of erythema multiforme in France, with emphasis on treatment choices. Br J Dermatol. 2018 Oct;179(4):1009-11.
6. Du Y, Wang F, Liu T, Jin X, Zhao H, Chen Q, et al. Recurrent oral erythema multiforme: a case series report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Apr;129(4):e224-e229.

7. Kempton J, Wright JM, Kerins C, Hale D. Misdiagnosis of erythema multiforme: a literature review and case report. Pediatr Dent. 2012;34:337-42.
8. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al; European Academy of Allergy and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014 Jul;69(7):868-87. doi: 10.1111/all.12313.
9. Alcântara CT, Raeder DFT, Campinhos FL, Brandão LS, Campos RA, Franca AT, et al. Guia Pratico de urticária aguda. Arq Asma Alerg Imunol.2022;6(2):214-24.
10. Charlton OA, Harris V, Phan K, Mewton E, Jackson C, Cooper A. Toxic Epidermal Necrolysis and Steven-Johnson Syndrome: A Comprehensive Review. Adv Wound Care (New Rochelle). 2020;9:426-39.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Sónia Pereira Garcia
E-mail: eugeniagarcia.med@gmail.com