Erythema multiforme

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Summary

Erythema multiforme is an inflammatory skin and mucosal disease mainly related to infectious agents such as Herpes simplex virus, *Mycoplasma pneumoniae*, though it can also be "idiopathic". The characteristic skin lesions are typical or atypical acral raised target lesions. The oral mucosa can be affected, alone or in combination with other mucosal/cutaneous sites, sometimes causing extreme pain, severely impacting food intake, and warranting hospitalization. A comprehensive understanding of erythema multiforme clinical characteristics, triggering agents, and differential diagnosis including Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, is crucial to conduct proper workup and management. *Mycoplasma pneumoniae* infection should be immediately ruled out because of the need of antibiotics. The cornerstone of management is symptomatic treatment and will be detailed in this review as well as the etiologic treatment. Lastly, the management of persistent or recurrent erythema multiforme can be challenging, especially when antivirals fail to prevent a relapse, but breakthrough treatments have been reported successful in this difficult-to-treat subset of patients.

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Introduction

Erythema multiforme (EM) is an inflammatory skin and mucosal disease mainly related to infectious agents such as Herpes simplex virus (HSV),[1] *Mycoplasma pneumoniae*[2,3] (MP), and less commonly other agents such as Poxviruses and Severe Acute Respiratory Syndrome -Coronavirus 2[4] (although some EM remain "idiopathic: see below). Epidemiological data of EM are scarce. The estimated prevalence ranges between 0.01% and 1%.[5] EM predominantly affects young adults, with a female preponderance, having a worldwide distribution without any ethnic predilection.[5] The clinical presentation is typically characterized by raised acral target lesions on the skin with sometimes mucous membranes involvement,[1,5] causing significant morbidity, impaired food intake, acute pain, hospitalization, and possible long-term sequelae.[6] The treatment is mainly symptomatic and the use of systemic corticosteroids remains debated.[1] The objective of this review is to detail a pragmatic approach to EM, focusing on the identification of triggers, red flags and management, providing a roadmap for future research. New concepts regarding nosology and severity will be provided as well.

Methods

Search strategy and selection criteria

On October 10th, 2023, search strategy and selection criteria data for this review were identified by searches of MEDLINE, PubMed, and references from relevant article using the following combination of search terms: "erythema multiforme" OR "EM" OR "Mycoplasma pneumonia induced rash and mucositis" OR MIRM OR "Reactive infectious mucocutaneous eruption" OR RIME. Candidate studies including brief reports and case reports were reviewed and articles about erythema multiforme, published only in English or French, were selected based on titles and abstracts. Abstracts and reports from meetings were included only when they related directly to previously published work. These

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candidate studies were obtained and read in full. Articles about drug-related Stevens-Johnson syndrome/toxic epidermal necrolysis, narrative reviews without any clinical patient data, and editorials were excluded (Fig. 1). The following data was obtained for analysis: triggers of EM, type of EM (minor or major), mucosal involvement, workup, histology findings, management strategies, mucosal sequelae and recurrence of the EM.

Role of funding source

None.

Nosology and definitions

Nosology

The first description of EM was reported by von Hebra in 1866 who described skin-limited lesions primarily localized on the extremities with a tendency to recur.[7] In 1983, Hoff et al. proposed the separation between EM "minor" and EM "major".[8] EM minor was defined as acute, self-limited, or episodic, symmetrically distributed, annular concentric erythematous skin lesions with absent mucosal lesions or lesions limited to 1 mucosal surface, while EM major had the same skin manifestations but with a more severe mucosal involvement, affecting two or more mucosal surfaces. Instead of the minor/major classification, categorization of EM according to severity is proposed to better guide the management. EM would be defined as severe or non-severe based on the degree of mucous membrane involvement. In severe EM, at least one mucous membrane would be heavily affected, e.g., oral mucosal involvement impairing food intake, with pain requiring opioid analgesics.

Recently, a distinct syndrome has been defined with MP, the so called *Mycoplasma pneumoniae*-induced rash and mucositis (MIRM).[2] Clinically, mucocutaneous eruptions in the MIRM are very morphologically diverse. They range from mucositis alone, to prominent

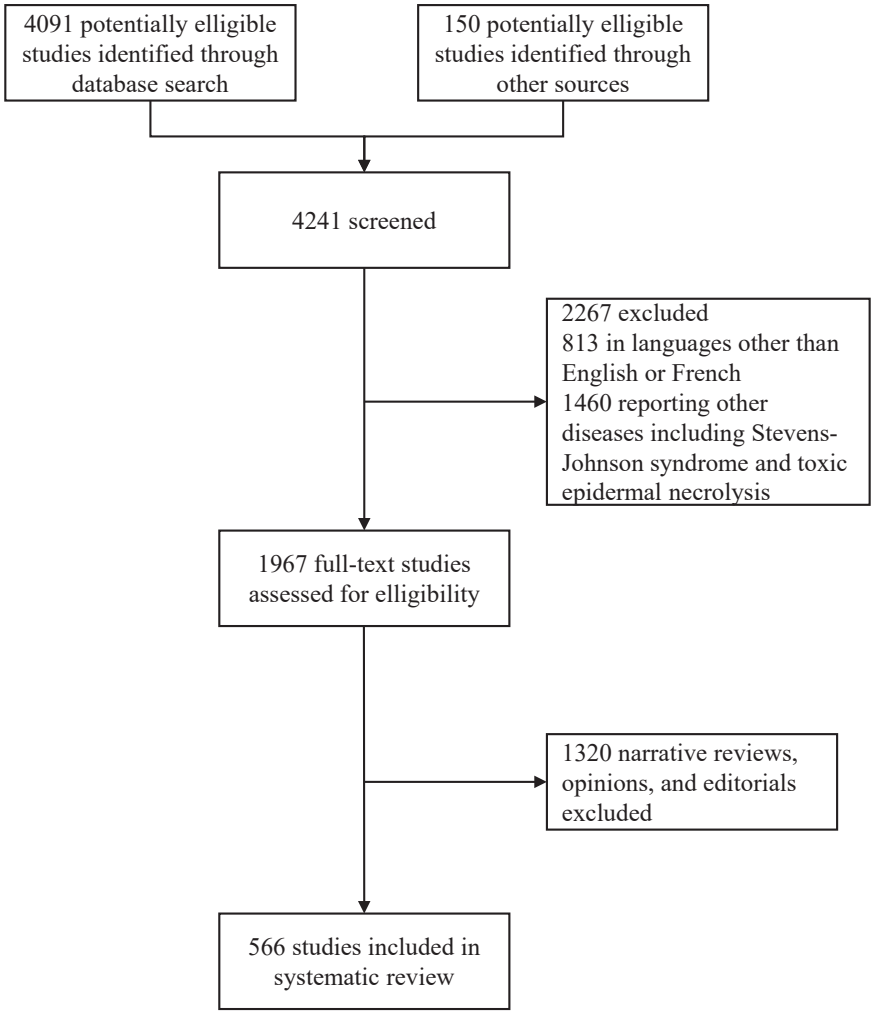

Fig. 1: **Study flowchart**.

mucositis with respiratory tract sequelae and little to moderate skin involvement.[3] Ramien et al.[9] proposed the umbrella term of reactive infectious mucocutaneous eruption (RIME) to acknowledge the multiple non-MP pathogens, including *Chlamydiae pneumoniae*, enterovirus, human metapneumovirus, human parainfluenzavirus 2, rhinovirus, adenovirus, and influenza B virus (Table 1). RIME encompasses several entities including the MIRM and infection-related severe EM.[9]

Whether MIRM/RIME is a separate entity, or a part of the EM spectrum is still a matter of debate. Clinical and histological findings of both strongly overlap with EM. Even though MP can induce epidermal necrolysis and some patients may have a sort of overlap between EM and Stevens-Johnson syndrome (SJS)/"Toxic" Epidermal Necrolysis (TEN) (Supplementary Figure S1).[10] Distinguishing between MIRM/RIME and SJS/TEN is of utmost importance as EM/RIME/MIRM and SJS/TEN warrant different management plans.[11]

While EM is most commonly caused by infections and SJS/TEN are most commonly caused by drugs, the clinical presentation is the determining factor in making the diagnosis of EM vs SJS/TEN. Typical or atypical raised target lesions are found in EM while purpuric macules evolving into vesicles, blisters and detachment are found in SJS/TEN (Supplementary Figures S1 and S2).[12] Skin detachment is usually limited in EM and the prognosis is generally better than SJS/TEN.[13] In fact, the final nosology is complex as an "Epidermal necrolysis" pattern may be found in both entities.

Potential triggers of EM	Potential triggers of RIME
HSV 1 and 2	***Mycoplasma pneumoniae***
Adenovirus	*Chlamydia* pneumoniae
CMV	Cytomegalovirus
EBV	Enterovirus/rhinovirus
Enterovirus	Epstein–Barr virus
Hepatitis B	Hepatitis A
Hepatitis C	HHV-6
HIV	Human metapneumovirus
Human metapneumovirus	Human parainfluenzavirus 2
Human parainfluenzavirus 2	Influenza B
Influenza B virus	Merckel cell Polyomavirus
Molluscum *contagiosum*	SARS-CoV2
Orf virus	Varicella Zoster virus
Rhinovirus	
SARS-CoV-2	
Varicella zoster virus	
Mycoplasma pneumoniae	
Borrelia burgdorferi	
Chlamydophila pneumoniae	
Gardenella vaginosis	
Neisseria meningitidis	
Treponema pallidum	
Tularemia	
Mycobacterium leprae	
Trichophyton mentagrophytes	
Microsporum canis	
Sporotrichosis	

Table 1: **Potential triggers of Erythema Multiforme (EM) and Reactive Infectious Mucocutaneous Eruption (RIME).**

Definitions

Acute EM flare: severe vs non-severe EM. Herein, instead of a major/minor classification, a more pragmatic approach based on the whole severity of the mucosal lesions is suggested, i.e. severe/non severe (see above).

Chronic EM. Chronic EM can be recurrent or persistent with recalcitrant lesions, worsening with flares. The repeated episodes of EM over a period of years are commonly defined as recurrent EM. In patients who suffer from recurrent EM, studies have reported an average of 6 episodes per year with a mean duration of 6–10 years.[14]

Persistent EM is defined as the continuous occurrence of typical or atypical raised target lesions without periods of complete healing.[5] Bullous lesions are often present. Mucosal lesions are not always constant in persistent EM.

Pathophysiology/etiology

The pathophysiology of EM is debated, and many points remain unanswered. The pathways leading to lesion formation in acute episodes of herpes-associated EM (HAEM) and MP-EM could differ from chronic EM (CEM). Compared to non-mycoplasma-related EM, it is hypothesized that mucosal lesion development is induced by direct injury of MP to the affected sites or indirect injury by immune complex-mediated vascular injury. The most studied pathway is that of the HAEM (Fig. 2).

Acute EM: the HAEM model

Several arguments illustrate the role of HSV in EM although the virus could not be isolated from skin lesions: i) the presence of viral DNA, ii) the expression of viral RNA and/or HSV antigens demonstrated not only in active skin lesions but also in the scarred skin several days after the acute episode. The most frequently expressed gene in skin lesions of patients with HAEM is the viral polymerase (pol) gene which may provide an aberrant DNA replication signal that results in altered cell cycle regulation and/or apoptosis. It could also stimulate a specific immune response in the skin. The healed HAEM lesional skin did not stain with pol antibody although the healed skin retained pol DNA suggesting that pol expression is associated with lesion development (Fig. 2).

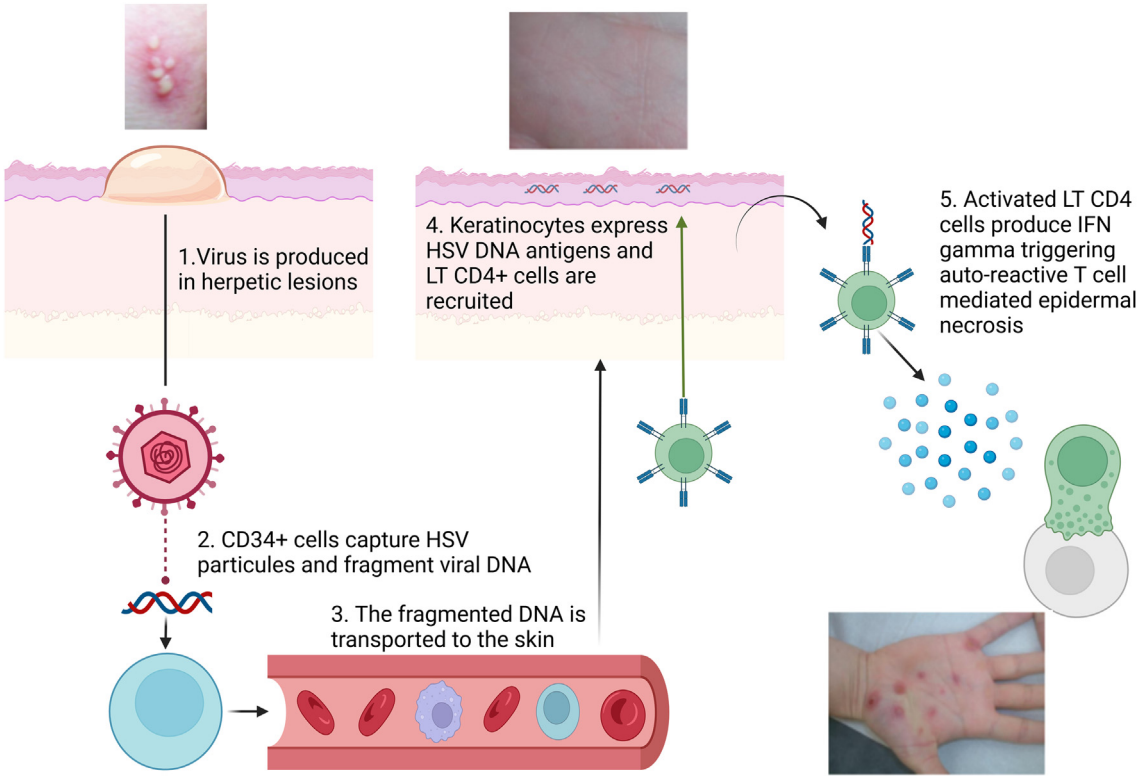

***Fig. 2:* Acute EM: the HAEM model**. *The virus is phagocytosed by macrophages and CD34+ Langerhans cells progenitors which are not permissive for HSV replication resulting in viral DNA fragmentation in HSV lesions. Whereas CD34+ cells from normal subjects or from patients with HSV infection but not HAEM evidenced a time-dependent loss of viral DNA that was no longer seen at 7 days post infection, by contrast CD34+ cells from HAEM patients were impaired in viral DNA clearance, thereby providing a unique opportunity for its delivery to the skin. These viral DNA fragments are transported by the CD34+ cells to distant keratinocytes and mucosal epithelia through upregulation of adhesion molecules such as E-cadherin.*[15,16] *The expression of HSV antigens results in the recruitment of CD4+ T helper type 1 cells with a subsequent release of IFN gamma and autoreactive T-cell mediated epidermal necrosis.*[17,18]

Persistent CEM

TNF has been demonstrated to be only weakly positive in EM lesions.[19,20] However, the possible efficacy of thalidomide and adalimumab in persistent EM suggested that inhibiting systemic TNF release might be a clue in the pathogenesis (rather than the local lesional effects).[19–21] Moreover the successful treatment of EM by inhibiting Janus kinase (JAK) suggests that JAK-signal transducer and activator of transcription (STAT) might also plays a role.[22] In fact, RNA sequencing and proteomic evaluation demonstrated that JAK-STAT dependent cytokines IFN-γ and interleukin (IL)-15 are upregulated in EM lesions and decrease with JAK inhibition.[22] These findings provide compelling evidence that EM is a CD8+ and NK T-cell–driven disease dependent on IFN-γ and IL-15 activation.[23] The TNF receptors on immune cells can activate the JAK-STAT signaling and JAK-STAT activation enhances TNF activity, at least in macrophages. Therefore, the TNF and JAK-STAT pathways are likely interconnected and play an important role in the pathophysiology of persistent EM.[23]

Plakins (PLK) are structural proteins found in the desmosomal plaque, including desmoplakin (DSP) I/II, envoplakin (ENV), and periplakin (PPL).[24] These proteins are targeted by auto-antibodies in paraneoplastic pemphigus (PNP) or pulmonary idiopathic fibrosis.[24] From 1995 onwards, a subset of electron microscopy studies has shown the presence of anti-PLK antibodies (anti-PLK-Abs) in EM skin lesions.[25] The exact role of anti-PLK antibodies (anti-PLK-Abs) in the progression of the disease, whether they serve as the initial triggering event, contribute to the relapse process, or are merely fortuitously detected due to epitope spreading, is yet to be fully understood. They were mostly associated with relapsing and difficult-to-treat EM.[24]

Finally, genetic susceptibility to EM has been reported, recurrent EM being associated with the HLA-DQB1*0301, HLA-B35, HLA-B62,15 and HLA-DR5320 alleles.[5,26]

Etiology

Ninety percent of EM cases reported in the medical literature were triggered by infections with the most common triggering agent being HSV.[1,8,17,27] HSV1 is more frequently associated with EM than HSV2.[1] MP is the second most commonly associated infection after HSV.[1,3,5,8] Currently, the World Health Organization declared clusters of respiratory illness in children in northern China and worldwide, partly due to MP and COVID-19.[28] These clusters need to be followed closely as they might be associated in increasing incidences of EM. SARS-CoV-2 has been recently linked to EM. The reported patients classically developed EM lesions after COVID-19 classic symptoms. Most patients had only skin involvement with minimally symptomatic mucosal involvement. EM was not associated with worse outcome of the disease.[29] Medical literature has linked other infectious agents to the development of EM. They are listed in Table 1. Vaccinations were also reported as EM triggers, which include pneumococcal vaccinations,[30,31] measles-rubella,[32] smallpox,[33] rabies,[34] HPV,[35] rotavirus,[36] diphtheria-pertussis-tetanus,[37] meningitis,[38] Hepatitis A,[30] and Hepatitis B.[39] All available COVID-19 vaccines were associated with EM.[40] The range of disease onset after vaccination was 3 days to 2 weeks and the clinical pattern resembled the one following COVID-19 infection.

Pediatric EM may have similar triggers when compared to adults and with a comparable clinical presentation. In children, post vaccination EM, although rare, was reported with most vaccines currently used, including the covid-19 vaccines. The diagnosis was mainly clinical in reported cases of pediatric EM and biopsies were rarely done. Infantile EM is a much rarer condition with only 19 reported cases, most commonly with vaccines. Neither MP-EM nor mucosal membrane involvement were reported in infants with EM.[41]

The question of the drug causality in EM is complex and controversial for several reasons: i) SJS may be misclassified as EM; ii) the presence of a culprit drug is not synonymous of the phenotype, e.g., SJS/TEN or EM; iii) EM is known to be mainly infection-related and cases of SJS were misclassified as "drug-induced EM". Demouche et al. analyzed all EM cases reported in the French pharmacovigilance database and concluded that only 6% of evaluable reports would be probable drug-induced EM and other diagnosis were excluded.[42] Moreover, although rare, the definite drug involvement as a causative factor cannot be confirmed even if a drug intake precedes the EM eruption. An additional confounding factor is that infections can also cause true SJS/TEN. Finally, a report of a few drug-induced EM in a pharmacovigilance data base retrospective analysis does not provide any strong evidence and large epidemiologic reports are needed with strict inclusion criteria, excluding all cases of SJS/TEN.

Signs and symptoms

Prodromal symptoms of fatigue, malaise, and myalgia are common in severe EM. They develop a week before the onset of skin and mucosal manifestations of EM.[5] The diagnosis of EM is made by careful skin examination The typical raised EM target lesions are characterized by 3 concentric rings located acrally or disseminated[1]: variably bullous central portion succeeded by[2] a dark red zone surrounding center,[3] and a lighter edematous ring and finally erythema at the outer portion of the lesions (Supplementary Figure S2). EM lesions may later evolve into geographic, polycyclic and annular configurations. MP-EM has a distinctive clinical presentation.[43] It more often occurs in winter and presents with less acral/more truncal predominant skin manifestations, ranging from purpuric macules to vesicles and bullae.[3] It is often accompanied with a more severe mucositis causing longer hospital stays and more long-term sequelae compared with HAEM.[3,6] Of note, clinical and radiological signs of pneumoniae were not constantly present in MP-EM.[3] *M. pneumoniae* can also induce SJS and TEN.[44] MP EM/RIME/MIRM differs from SJS/TEN by predominantly affecting the mucosal surfaces involvement with variable skin involvement, younger patients, and better prognosis.[2,44] MIRM and RIME could be considered as part of the EM spectrum with severe involvement in general. Beyond the minor and major classification of EM, including the MIRM and RIME, focusing on the severity of EM is what matters in the management of the disease as mucosal involvement can be severe causing significant pain and reduced food intake for instance (see above).[1]

Mucosal involvement

The typical primary lesion of the oral mucosa consists of vesicles, but they rupture easily, giving way to post-bullous erosions. The initial mucosal lesions are rarely visualized. The onset of the disease is often brisk, preceded by tingling sensations in the affected areas. Lesions preferentially occur on non-keratinized mucous membranes such as the lips, cheeks, ventral surfaces of the tongue and are often painful. The gum is typically spared, allowing the differential diagnosis of primary herpetic infection, which is accompanied by general signs and symptoms, fever, and painful cervical lymph nodes. Involvement of the vermilion of both lips is common, with the presence of hemorrhagic crusts. Skin rosettes are inconsistent. The intensity of oral involvement varies; it can be minimal with few lesions, or, conversely, extremely extensive, preventing any food intake with subsequent hospitalization. Mucosal lesions spontaneously resolve within two to three weeks without leaving a scar. Outbreaks of oral erythema multiforme can recur at an unpredictable rate. Some patients will have only one outbreak in their lifetime, while others will have one to two per year. Conversely, some patients will have frequent or even continuous outbreaks. The

current body of research does not provide any evidence to explain why patients differ in the frequency of outbreaks from once in lifetime to annually or continuous EM flare-ups. In HSV-induced EM some patients will only have one episode while others will have recurrences every month. HSV lesions do not always precede EM. The diagnosis is confirmed when long term suppressive antiviral therapy reduces the EM flares. The prognosis of oral erythema multiforme is dominated by the frequency of these recurrences, making this condition sometimes disabling, warranting a preventive treatment.

Oral EM

Isolated oral EM is a subset of EM that presents with clinical features of multiple self-limited irregular oral ulcers. The disease can be recurrent. HSV is the most common triggering agent. The diagnosis is challenging and is based on the exclusion of other mucosal diseases such as auto-immune bullous diseases, erosive mucosal lichen planus, and SJS, rendering the biopsy a crucial step in management. The current epidemiologic data is not enough to support this phenotype but in our experience, cases of isolated oral EM lesions without any skin manifestations, in the absence of drug intake and after ruling out auto-immune bullous diseases and connective tissue diseases by serology and/or biopsy would be considered and treated as EM.[45–47]

Pathological findings

Different pathological findings have been reported, possibly due to varying degrees of skin involvement severity, underlying infections, and/or the exact site of the skin biopsy (e.g., center vs periphery of targetoid lesions).[3] Most EMs present with an interface dermatitis, characterized by a mild to moderate dermal infiltrate of lymphocytes, also infiltrating the basal layers of the epidermis, and associated with basal vacuolar changes and scattered apoptotic keratinocytes readily involving the suprabasal layers (Supplementary Figure S3). Spongiosis and edema of the papillary dermis are sometimes present.[48] Histologically, EM can present as epidermal necrolysis with confluent keratinocyte apoptosis and epidermal detachment as shown in (Supplementary Figure S3). This is thought to be more common in MP-infected patients.[3,49] Because of these different histopathological aspects, dermal (dermal papillary edema and inflammation with minimal epidermal injury), epidermal (marked epidermal lesions and apoptosis), and mixed forms are classically described. They correspond more or less to the more recently described maculo-papular exanthema (MPE)-like and TEN-like forms.[3]

Dermal infiltrates are composed of lymphocytes, including coarse-grained lymphocytes, and some macrophages.[48] Eosinophils and neutrophils may also be present.[3,50,51] Plasmacytoid dendritic cells are thought to be more abundant in virus-associated and recurrent cases.[52,53] Direct immunofluorescence studies generally show nonspecific results: labeling of apoptotic bodies, granular deposition of C3 along the dermoepidermal junction and in papillary dermal vessels.[54,55] The presence of properdin suggests activation of the alternative complement pathway.[55]

EM resembles other skin conditions manifesting as an interface dermatitis. TEN-like forms are morphologically indistinguishable from various histological simulators manifesting as an « acute syndrome of apoptotic pan-epidermolysis », a concept first introduced by Ting et al.[56]: lupus-Lyell and Rowell syndrome, TEN/SJS, generalized fixed bullous drug eruption, severe graft-vs-host disease (GVHD), Nigella sativa oil-induced toxicity and certain infectious dermatoses such as foot-hand-mouth syndrome. The expression profile of Desmoplakin I/II nevertheless appears to differ in ME and GVHD, SJS and TEN.[25,57] The acrosyringeal localization of apoptotic keratinocytes and the presence of dermal eosinophils would suggest a drug-induced etiology.[58] Finally, it has been shown that adult hand-foot-mouth syndrome is associated with more neutrophils and pustules.[59]

Workup

The diagnostic workup for EM may vary based on the clinical context, severity of symptoms, and individual patient characteristics and comorbidities (Fig. 3). When EM is suspected, a comprehensive evaluation of the patient's medical history and drug intake is conducted, focusing on the characteristics, distribution, and progression of skin and mucosal lesions. Physical examination includes a meticulous inspection of the lesions to determine their morphology, extent, and severity. Notable details regarding associated symptoms, recent infections, drug exposure, or potential triggers are recorded. All the mucosal membranes should be examined, including the ocular, oral and anal and genital mucosae. Food and water intake should be assessed as well as a complete pulmonary examination to rule out associated lung disease. Esophageal involvement should be investigated if appropriate. Skin and mucous membrane biopsies may be obtained to confirm the diagnosis. Suspicious skin and mucosal lesions, indicative of HSV infection, should be sampled for Tzanck smear, PCR studies, or viral culture to rule out HSV infection. All patients presenting with severe EM should undergo a complete lung examination, a chest radiograph and if possible, PCR testing of throat swabs, and serologic tests for MP. Diagnosis is usually confirmed by the presence of IgM antibodies or a significant increase (greater than two-fold) in IgG antibodies. Recurrent episodes of EM have been linked to recurrent HSV infections, but the great majority of cases HSV and EM occurrence were not parallel. However, it's important to note that

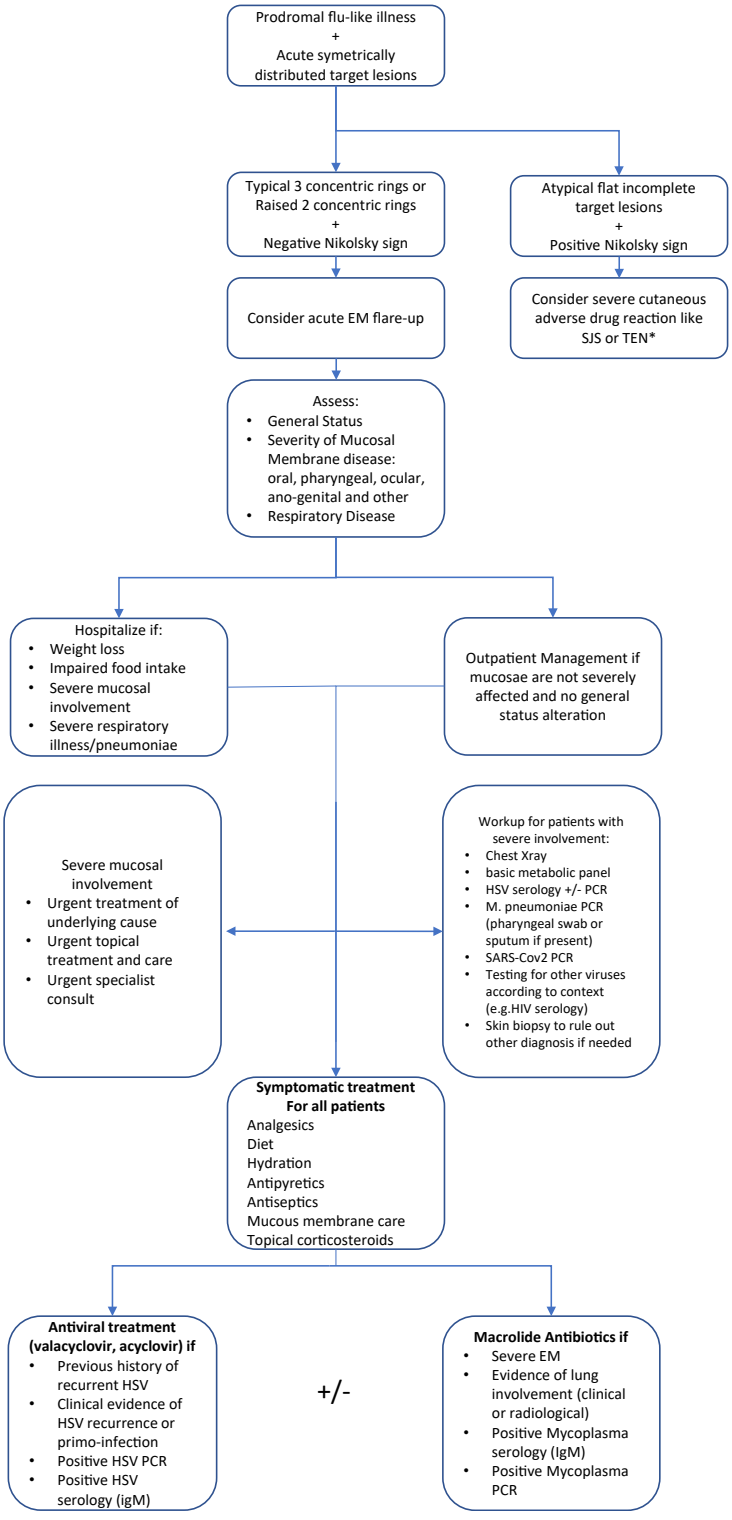

***Fig. 3:* Management algorithm of first EM episode**. *Compared to HSV-associated EM, Mycoplasma-pneumoniae induced more diffuse EM lesions, more mucositis and respiratory tract sequelae; therefore, prompt detection of MP and systematic early antibiotic treatment could improve the course of the disease. MM: mucous membrane. Systemic corticosteroids were not included in the treatment algorithm of a severe acute EM flare as their potential role will be determined by an ongoing RCT. *SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis.*

antibody titers are not reliable for detecting recurrent episodes of the disease.[15]

Treatment and prognosis

Treatment of first acute EM episode

The mainstay of therapy involves identifying and treating the causative agent, if possible as well as providing supportive care to the disease, prevent complications and mucosal sequelae. Mucosal pain, food intake, weight loss and other systemic symptoms should be evaluated to assess the need for hospitalization.[1,5] There are no validated tools specific for EM but the general tools to measure pain like the numeric rating scale and food intake can be used for follow-up and for research purposes (Fig. 4).

Supportive care and symptom control. There is no consensus on supportive care in EM mucosal lesions. Due to the similarities of the mucosal lesions and functional consequences in SJS/TEN and EM, supportive care would be comparable.[60] The standard-of-care treatment firstly relies on: analgesics, including opioids, antipyretics, antiseptics, and mucous membrane care. Vaseline or other moisturizing ointment should be applied twice a day on skin lesions. Topical corticosteroids may also be considered to control the skin lesions.[5,41,61]

The symptomatic treatment of mucous membranes consists of antiseptic and analgesic mouthwashes composed of chlorhexidine or with corticosteroids, mycostatin, lidocaine and bicarbonate mouthwashes every 4 h, and lidocaine gel before meals for the oral mucosae, artificial tears without preservative, and vitamin A ointment for the eyes; Vaseline for the genital membranes. If the patient presents with severe pain, opioids can be prescribed and if oral intake is severely affected, diet adapted to the ability to eat/drink, hydration with a gastric feeding tube if needed.

The use of Systemic Corticosteroid (SCS) during the established phase of severe EM remains a topic of debate and lacks standardized guidelines. Most current studies are retrospective and rely on small cohorts or case reports.[1,41] They would have a potential interest in alleviating pain with quicker symptom control in severe EM. We recently conducted a multicenter retrospective national study showing that in routine practice, SCS were prescribed for 15.5% of hospitalized patients with severe EM with doses ranging from 0.5 to 1 mg/kg/day with a rapidly decreasing dosage over 10–15 days. However, because of the retrospective design of the study, we failed to strongly demonstrate the benefit of SCS in reducing the length of hospital stay, control of pain or impaired food intake.[1] To properly evaluate the benefits of SCS in this disease and provide robust guidance to clinicians, an academic randomized controlled trial is currently planned (NCT06266221).

Etiological treatment. In EM, especially severe EM, macrolide antibiotics should be systematically prescribed[61–65] (Fig. 3). They would be continued if a MP infection is confirmed, otherwise they would be stopped. In suspected HAEM, antivirals do not alter the

Pain Numeric Scale

0 Impossible	1 +/- Liquid	2 Blended	3 Chopped	4 Solid
nothing			Bread, ruskis, soft bread, croissants…	
	Soup Drinks (water, fruit juice, coffee, tea, herbal teas…) Milk	Appetizers (blended) or soft deli meat (such as liver mousse)	Tender raw vegetables (tomatoes, beets) No hard raw foods such as cucumber or green salad) Deli meats (cold cuts)	All raw vegetables
		Meat, fish and eggs	Minced meat Ham, fish, eggs (whole)	All whole meats
		Mashes (potatoes / vegetables)	Whole cooked vegetables and starchy staple foods	All raw and cooked vegetables
	Fluid dairy products (yoghurts, white cheeses …)	Dairy products without chunks or cheese spreads	All cheeses and dairy products	
	Fluid dessert creams, compotes	Compotes, Desserts without chunks (creamy type)	Fruits in syrup Ripe raw fruits (except apples) Pastry	All raw fruits
	ONS liquids	ONS creams		

ONS: Oral Nutritional Supplements
Each column lists foods that are in addition to the previous column.
One food in the next column is enough to switch to the next level.

Food intake rating scale

Fig. 4: **Suggested tools to measure pain and food intake in EM.**

course of the acute episode and are only useful as a prophylactic regimen (see below).[1,5]

Treatment of recurrent EM

The preventive treatment of recurrent (EM) poses significant challenges and often requires prolonged therapy. In cases of HAEM and idiopathic recurrent EM, continuous or intermittent antiviral therapy is the first line approach.[14,66] The most effective approach was continuous antiviral therapy for a duration of at least six months (acyclovir [400 mg twice daily], valacyclovir [500 mg twice daily] or famciclovir [250 mg twice daily]).[67] The primary treatment objective is to reduce the frequency of EM episodes and achieve clinical remission. In cases where EM does not respond to initial treatment, the medication dose may be increased, or an alternative antiviral drug may be substituted. Unfortunately, maintaining remission is challenging even with treatment.[68,69] Generally, patients who respond to continuous antiviral therapy should be treated for 1–2 years before considering potential discontinuation. If EM recurs after discontinuation, medication should be restarted at the lowest effective dose, and therapy cessation may be attempted again in 6–12 months.[5] As a note, the efficacy of antivirals demonstrates *a posteriori* the HSV cause of EM.

Limited evidence exists for the continuous administration of alternative treatments in cases of recurrent EM that do not respond to antivirals representing second-line treatment options.[69] Among these treatments, thalidomide,[20] lenalidomide,[70] immunoglobulins,[68] and azathioprine[66] have shown higher rates of complete remission (80%). However, these findings are based on small patient cohorts (Table 1). Dapsone and mycophenolate mofetil have demonstrated complete response rates in one-third of patients, while antimalarials and colchicine have shown limited or no response, respectively.[69]

Treatment of persistent EM

Emerging research indicates the potential benefits of alternative immunomodulatory agents, such as biologic agents, including thalidomide, anti-tumor necrosis factor (TNF) agents, apremilast, rituximab, and JAK inhibitors[71] that have shown promising results in the management of severe and refractory cases of EM.[72] (Table 2) Thalidomide was shown to be effective in both, suggesting a common physiopathology to some extent.[20] In persistent EM, a retrospective case-series have shown favorable results with thalidomide (62% remission rate at 6 months of treatment). The starting dose was 50 mg daily followed by a decreased dosage after complete remission at 6 months to minimize side effects and neuropathy.[20] Jak-inhibitors such as upadacitinib or tofacitinib can be effective for persistent EM.[71,72] Molecular and cytokine analysis could be effective in characterizing chronic EM phenotypes to help target the dominant inflammatory pathway, maximizing clinical outcomes.[22]

Although further studies are warranted to establish long-term efficacy and safety profiles, these targeted therapeutic options hold potential for improving outcomes in patients with EM.

Author, year of publication	Patients (n)	Type of EM	Treatment received	Complete response n/N (%)	Partial response n/N (%)
Cherouati 1996; Oliveira 2021; Roux 2021, Zhou 2021, Roux 2021	49	Recurrent	Thalidomide	51/71 (72)	1/71 (2)
Oak 2016; Schofield 1993; Wetter 2010; Oliveira 2021	40	Recurrent	Dapsone	18/40 (45)	7/40 (18)
Schofield 1993; Wetter 2010	15	Recurrent	Azathioprine	12/15 (80)	2/15 (13)
Schofield 1993; Wetter 2010	13	Recurrent	Immunoglobulins	2/13 (15)	2/13 (15)
Schofield 1993; Wetter 2010	8	Recurrent	Mycophenolate mofetil	3/8 (38)	3/8 (38)
Oro 2023	7	Recurrent	Lenalidomide	6/7 (85)	
Miller 2021	6	RIME	Etanercept	6/6 (100)	
Schofield 1993; Wetter 2010	5	Recurrent	Colchicine	0/5 (0)	5/5 (100)
Roux 2021	13	Persistent	Thalidomide	8/13 (61.5)	
Hirsch 2016	5	Persistent	Rituximab	4/5 (80)	
Murphy 2021	4	Persistent	Tofacitinib	1/4 (25)	3/4 (75)
Chen 2017	3	Recurrent	Apremilast	3/3 (100)	
Deutsch 2023	1	Persistent	Upadacitinib	1/1	
Lee 2023	1	Persistent	Upadacitinib	1/1	

Table 2: **Immunomodulatory therapy of chronic EM.**

Conclusion

EM is a well-defined entity, with typical and atypical cutaneous and mucous manifestations that can sometimes be severe, warranting hospitalization. Various triggers, mainly HSV and MP, have been linked to EM. EM can affect adults as well as the pediatric population. Prompt recognition and early intervention are critical, hence the importance of increasing awareness among general practitioners, emergency physicians, pediatricians as well as intensivists. The curative role of SCS in severe EM is not determined yet. Recurrent persistent EM is a challenge and should be referred to specialized dermatologists. Further studies are needed to shed light on the molecular pathways behind the different mucocutaneous eruptions associated with MP, and the role of Jak-inhibitors in the management of EM.

Outstanding questions

This review provides a roadmap for future research, as many outstanding questions remain unanswered.

A large validation of the definitions of EM, e.g., severe vs non severe, EP vs MIRM/RIME, drug-related EM, atypical EM vs typical EM, oral mucosal EM would be very helpful.

MP was associated with EM/RIME and true SJS/TEN. Molecular analysis is warranted to determine whether the pathophysiological pathway is common or different in these entities. Further research is needed to shed light on the mechanisms implicated in MP-induced EM vs MP-induced TEN.

More evidence is needed to clarify the mechanisms of the highly variable frequency of outbreaks ranging from once in a lifetime to multiple/continuous recurrences.

A RCT evaluating the value of SCS in severe EM is mandatory.

Jak-inhibitor have been proven efficient in case-series. Larger prospective trials are needed to confirm the efficacy of Jak-inhibitors in the treatment of recurrent EM.

Contributors

All authors read and approved the final version of the manuscript.

Elio Kechichian: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, visualisation, writing—original draft, and writing—review & editing.

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Declaration of interests

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102909.

References

1 Kechichian E, Ingen-Housz-Oro S, Sbidian E, et al. A large epidemiological study of erythema multiforme in France, with emphasis on treatment choices. *Br J Dermatol*. 2018;179(4):1009–1011.
2 Canavan TN, Mathes EF, Frieden I, Shinkai K. Mycoplasma pneumoniae-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: a systematic review. *J Am Acad Dermatol*. 2015;72(2):239–245.
3 Amode R, Ingen-Housz-Oro S, Ortonne N, et al. Clinical and histologic features of Mycoplasma pneumoniae-related erythema multiforme: a single-center series of 33 cases compared with 100 cases induced by other causes. *J Am Acad Dermatol*. 2018;79(1):110–117.
4 Etaee F, Eftekharian M, Naguib T, Daveluy S. Erythema multiforme in COVID-19 patients and following COVID-19 vaccination: manifestations, associations and outcomes. *J Eur Acad Dermatol Venereo*. 2022;36(7):e524–e530.
5 Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol*. 2012;51(8):889–902.
6 Viarnaud A, Ingen-Housz-Oro S, Marque M, et al. Severe sequelae of erythema multiforme: three cases. *J Eur Acad Dermatol Venereo*. 2018;32(1):e34–e36.
7 Hebra F. *Atlas der Hautkrankheiten*. Aus der kaiserlich-königlichen Hof- und Staatsdruckerei; 1856 [book].
8 Clark Huff J, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*. 1983;8(6):763–775.
9 Ramien ML, Bruckner AL. Mucocutaneous eruptions in acutely Ill pediatric patients—think of mycoplasma pneumoniae (and other infections) first. *JAMA Dermatol*. 2020;156(2):124–125.
10 Heymann WR. More than Mycoplasma-induced rash and mucositis: the potential role of Mycoplasma pneumoniae in Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Am Acad Dermatol*. 2022;86(4):746–747.
11 Mulvey JM, Padowitz A, Lindley-Jones M, Nickels R. Mycoplasma pneumoniae associated with Stevens Johnson syndrome. *Anaesth Intensive Care*. 2007;35(3):414–417.
12 Ingen-Housz-Oro S, Ortonne N, Chosidow O. The diagnosis is in the rings. *BMJ*. 2017;359:j3817.
13 Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet Lond Engl*. 2017;390(10106):1996–2011.
14 Dias de Oliveira NF, Miyamoto D, Maruta CW, Aoki V, Santi CG. Recurrent erythema multiforme: a therapeutic proposal for a chronic disease. *J Dermatol*. 2021;48(10):1569–1573.
15 Aurelian L, Kokuba H, Burnett JW. Understanding the pathogenesis of HSV-associated erythema multiforme. *Dermatol Basel Switz*. 1998;197(3):219–222.
16 Caproni M, Torchia D, Schincaglia E, et al. The CD40/CD40 ligand system is expressed in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. *Br J Dermatol*. 2006;154(2):319–324.
17 Weston WL. Herpes-associated erythema multiforme. *J Invest Dermatol*. 2005;124(6):xv–xvi.
18 Ng PPL, Sun YJ, Tan HH, Tan SH. Detection of herpes simplex virus genomic DNA in various subsets of Erythema multiforme by polymerase chain reaction. *Dermatol Basel Switz*. 2003;207(4):349–353.
19 Drahy F, Ingen-Housz-Oro S, Grootenboer-Mignot S, Wolkenstein P, Chosidow O. Lenalidomide as an alternative to thalidomide for treatment of recurrent erythema multiforme. *JAMA Dermatol*. 2018;154(4):487–489.
20 Roux C, Sbidian E, Bouaziz JD, et al. Evaluation of thalidomide treatment of patients with chronic erythema multiforme: a multicenter retrospective cohort study. *JAMA Dermatol*. 2021;157(12):1472–1476.
21 Baillis B, Maize JC. Treatment of recurrent erythema multiforme with adalimumab as monotherapy. *JAAD Case Rep*. 2017;3(2):95–97.
22 Murphy MJ, Gruenstein D, Wang A, et al. Treatment of persistent erythema multiforme with Janus kinase inhibition and the role of interferon gamma and interleukin 15 in its pathogenesis. *JAMA Dermatol*. 2021;157(12):1477–1482.
23 Dominguez AR, Lopez SN. Novel treatments for chronic erythema multiforme inform translational science and disease pathogenesis. *JAMA Dermatol*. 2021;157(12):1411–1413.
24 Weill A, Descamps V, Chasset F, et al. Erythema multiforme associated with anti-plakin antibodies: a multicentric retrospective case series. *J Eur Acad Dermatol Venereo*. 2022;36(12):2438–2442.
25 Irwin T, Yeung CCS, Shinohara MM. Desmoplakin I/II immunohistochemical staining may be a helpful tool in differentiating cutaneous graft versus host disease from the erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis spectrum disorders. *J Cutan Pathol*. 2024;51(1):76–82.
26 Khalil I, Lepage V, Douay C, et al. HLA DQB1*0301 allele is involved in the susceptibility to erythema multiforme. *J Invest Dermatol*. 1991;97(4):697–700.
27 Hosaka H, Ohtoshi S, Nakada T, Iijima M. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: frozen-section diagnosis. *J Dermatol*. 2010;37(5):407–412.
28 WHO statement on reported clusters of respiratory illness in children in northern China [cited 2024 Feb 5]. Available from: https://www.who.int/news/item/22-11-2023-who-statement-on-reported-clusters-of-respiratory-illness-in-children-in-northern-china.
29 Daneshgaran G, Dubin DP, Gould DJ. Cutaneous manifestations of COVID-19: an evidence-based review. *Am J Clin Dermatol*. 2020;21(5):627–639.

30 Hernandez Quiroz E, Kauffman CL, Kupiec-Banasikowska A. Erythema multiforme following hepatitis A and pneumococcal vaccinations. *Yale J Biol Med*. 2022;95(2):213–215.
31 Monastirli A, Pasmatzi E, Badavanis G, Tsambaos D. Erythema multiforme following pneumococcal vaccination. *Acta Dermatovenerol Alp Pannonica Adriat*. 2017;26(1):25–26.
32 Oka M. Simultaneous development of gianotti-crosti syndrome and erythema multiforme following second dose of measles-rubella vaccine. *Acta Derm Venereol*. 2021;101(4):adv00438.
33 Storie EB, Perry A. Erythema multiforme following smallpox vaccination. *Mil Med*. 2014;179(1):e113–e115.
34 Verma P. Erythema multiforme possibly triggered by rabies vaccine in a 10-year-old boy. *Pediatr Dermatol*. 2013;30(6):e297–e298.
35 Katoulis AC, Liakou A, Bozi E, et al. Erythema multiforme following vaccination for human papillomavirus. *Dermatol Basel Switz*. 2010;220(1):60–62.
36 Kim JJ, Lee JK. Neonatal erythema multiforme associated with a rotavirus infection: a case report. *World J Clin Cases*. 2023;11(24):5749–5754.
37 Karincaoğlu Y, Aki T, Erguvan-Onal R, Seyhan M. Erythema multiforme due to diphtheria-pertussis-tetanus vaccine. *Pediatr Dermatol*. 2007;24(3):334–335.
38 Studdiford J, Oppenheim L, McCann E, Altshuler M. Erythema multiforme after meningitis vaccine: patient safety concerns with repeat immunization. *Pharmacotherapy*. 2006;26(11):1658–1661.
39 Wine E, Ballin A, Dalal I. Infantile erythema multiforme following hepatitis B vaccine. *Acta Paediatr Oslo Nor*. 2006;95(7):890–891.
40 Yousefian M, Khadivi A. Occurrence of erythema multiforme following COVID-19 vaccination: a review. *Clin Exp Vaccine Res*. 2023;12(2):87–96.
41 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(3):813–822.
42 Demouche S, Bettuzzi T, Sbidian E, et al. Reality of drug-induced erythema multiforme: a French pharmacovigilance study. *Therapies*. 2023;78(6):711–719.
43 Valle J, Nasrollahi F, Eilbert W. Mycoplasma pneumoniae-induced rash and mucositis. *Am J Emerg Med*. 2022;54:324.e5–324.e7.
44 Liew YCC, Choo KJL, Oh CC, Pang SM, Yeo YW, Lee HY. Mycoplasma-induced Stevens-Johnson syndrome/toxic epidermal necrolysis: case-control analysis of a cohort managed in a specialized center. *J Am Acad Dermatol*. 2022;86(4):811–817.
45 Bean SF, Quezada RK. Recurrent oral erythema multiforme. Clinical experience with 11 patients. *JAMA*. 1983;249(20):2810–2812.
46 Lozada-Nur F, Gorsky M, Silverman S. Oral erythema multiforme: clinical observations and treatment of 95 patients. *Oral Surg Oral Med Oral Pathol*. 1989;67(1):36–40.
47 Du Y, Wang F, Liu T, et al. Recurrent oral erythema multiforme: a case series report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;129(4):e224–e229.
48 Orfanos CE, Schaumburg-Lever G, Lever WF. Dermal and epidermal types of erythema multiforme. A histopathologic study of 24 cases. *Arch Dermatol*. 1974;109(5):682–688.
49 Ford MJ, Smith KL, Croker BP, Hacker SM, Flowers FP. Large granular lymphocytes within the epidermis of erythema multiforme lesions. *J Am Acad Dermatol*. 1992;27(3):460–462.
50 Patterson JW, Parsons JM, Blaylock WK, Mills AS. Eosinophils in skin lesions of erythema multiforme. *Arch Pathol Lab Med*. 1989;113(1):36–39.
51 Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol*. 1996;135(1):6–11.
52 Finan MC, Schroeter AL. Cutaneous immunofluorescence study of erythema multiforme: correlation with light microscopic patterns and etiologic agents. *J Am Acad Dermatol*. 1984;10(3):497–506.
53 Dias de Oliveira NF, Santi CG, Maruta CW, et al. Increased expression of in situ CD123 and reduced Toll-like receptor 7/9 signalling pathway suggest impaired activation of plasmacytoid dendritic cells in recurrent erythema multiforme. *J Eur Acad Dermatol Venereol*. 2024;38(9):e816–e819.
54 Imamura S, Yanase K, Taniguchi S, Ofuji S, Mangaoil L. Erythema multiforme: demonstration of immune complexes in the sera and skin lesions. *Br J Dermatol*. 1980;102(2):161–166.
55 Grimwood R, Huff JC, Weston WL. Complement deposition in the skin of patients with herpes-associated erythema multiforme. *J Am Acad Dermatol*. 1983;9(2):199–203.
56 Ting W, Stone MS, Racila D, Scofield RH, Sontheimer RD. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus and the spectrum of the acute syndrome of apoptotic pan-epidermolysis (ASAP): a case report, concept review and proposal for new classification of lupus erythematosus vesiculobullous skin lesions. *Lupus*. 2004;13(12):941–950.
57 Forrester VJ, Tran B, Hein SC, Wick MR. Pattern-specific loss of desmoplakin I and II immunoreactivity in erythema multiforme and its variants: a possible aid in histologic diagnosis. *Am J Dermatopathol*. 2020;42(2):111–116.
58 Zohdi-Mofid M, Horn TD. Acrosyringeal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology. Clinicopathologic review of 29 cases. *J Cutan Pathol*. 1997;24(4):235–240.
59 Böer-Auer A, Metze D. Histopathology of hand-foot-mouth disease in adults and criteria for differentiation from erythema multiforme. *Am J Dermatopathol*. 2019;41(4):273–280.
60 Ingen-Housz-Oro S, Duong TA, Bensaid B, et al. Epidermal necrolysis French national diagnosis and care protocol (PNDS; protocole national de diagnostic et de soins). *Orphanet J Rare Dis*. 2018;13:56.
61 Gise R, Elhusseiny AM, Scelfo C, Mantagos IS. Mycoplasma pneumoniae-induced rash and mucositis: a longitudinal perspective and proposed management criteria. *Am J Ophthalmol*. 2020;219:351–356.
62 Narita M. Classification of extrapulmonary manifestations due to mycoplasma pneumoniae infection on the basis of possible pathogenesis. *Front Microbiol*. 2016;7:23.
63 Schalock PC, Dinulos JGH. Mycoplasma pneumoniae-induced cutaneous disease. *Int J Dermatol*. 2009;48(7):673–680.
64 Brazel D, Kulp B, Bautista G, Bonwit A. Rash and mucositis associated with mycoplasma pneumoniae and chlamydophila pneumoniae: a recurrence of MIRM? *J Pediatr Infect Dis Soc*. 2021;10(2):220–224.
65 Mayor-Ibarguren A, Feito-Rodriguez M, González-Ramos J, et al. Mucositis secondary to Chlamydia pneumoniae infection: expanding the mycoplasma pneumoniae-induced rash and mucositis concept. *Pediatr Dermatol*. 2017;34(4):465–472.
66 Wetter DA, Davis MDP. Recurrent erythema multiforme: clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. *J Am Acad Dermatol*. 2010;62(1):45–53.
67 Tatnall FM, Schofield JK, Leigh IM. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol*. 1995;132(2):267–270.
68 Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol*. 1993;128(5):542–545.
69 de Risi-Pugliese T, Sbidian E, Ingen-Housz-Oro S, Le Cleach L. Interventions for erythema multiforme: a systematic review. *J Eur Acad Dermatol Venereo*. 2019;33(5):842–849.
70 Ingen-Housz-Oro S, Joly P, Kini-Matondo W, Sbidian E. Prevention of recurrent erythema multiforme with lenalidomide: a case series. *Clin Exp Dermatol*. 2023:llad314.
71 Lee JM, Lee YJ, Choi YJ, Lee JH, Choi JE, Han TY. A case of persistent erythema multiforme treated with upadacitinib. *J Dermatol*. 2020;n/a(n/a) [cited 2023 Oct 12]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/1346-8138.16938.
72 Deutsch A, Rodriguez N, Roy S, Leventhal JS. Treatment of persistent erythema multiforme with upadacitinib: a novel therapeutic approach. *JAAD Case Rep*. 2023;34:70–73.