Erythema Multiforme

A Review of Epidemiology, Pathogenesis, Clinical Features, and Treatment

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KEYWORDS

• Erythema multiforme • Oral ulcer • Vesiculobullous • Immune disorder • Ulcerative • Stevens–Johnson syndrome

KEY POINTS

- Erythema multiforme (EM) is a widespread hypersensitivity reaction that occurs with varying degrees of severity.
- Herpes simplex virus (HSV) infection is the most common precipitator of EM, and the possibility of HSV-induced disease should be considered in all patients.
- The history of lesion eruption and related clinical findings provides the most important information for the diagnosis of EM. Patients should be queried regarding prodromal symptoms as well as recent introduction of any new medications.
- The clinical course of EM is usually self-limiting, resolving within weeks without significant sequelae. However, in a minority of cases, the disease recurs frequently over the course of years.
- Most patients with EM can be managed with symptomatic therapy alone. However, patients with severe EM may require hospitalization for hydration, analgesia, antiviral therapy, and systemic steroids.

INTRODUCTION

Erythema multiforme (EM) may be seen in the dental setting, and the acute onset of the condition results in the need for prompt diagnosis and care. This acute immune-mediated disorder affects the skin and/or mucous membranes, including

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the oral cavity.[1] It is a blistering, ulcerative, mucocutaneous condition that is characterized by target or iris lesions distributed symmetrically on the extremities and trunk.[2] EM has a wide spectrum of clinical manifestations that may be triggered by hypersensitivity reactions to various antigens and has a tendency to recur.[3,4] Clinical classification of EM is typically based on the severity of the condition, including EM minor (EMm) and EM major (EMM).[5] Similarities in clinical and histopathologic findings have led to controversy over the distinction between EM and Steven Johnson syndrome (SJS). However, there is increasing evidence to suggest that EM is a condition distinct from SJS and toxic epidermal necrolysis (TEN) due to differences of potential causes, clinical presentation, patient demographics, and pathology.[6,7] The purpose of this article is to review the epidemiology, pathogenesis and clinical features of erythema multiforme and to discuss the importance of early diagnosis and prompt treatment of the condition.

EPIDEMIOLOGY

The reported epidemiologic data related to EM is scarce. This is likely because of the acute nature of the condition, the absence of a universally accepted classification system, and the lack of a reporting registry. The reported prevalence rate of erythema multiforme is less than 1%.[8] A summary of the overall incidence of hospitalization for EM is documented in **Table 1**.

EM typically occurs in young adults 20 to 40 years of age[9] and is more common in women compared with men (1.5:1.0).[10] There is a reported recurrence rate of 37%[11] and a genetic predisposition to certain Asian ethnic groups.[12] Prevalence rates of oral EM lesions vary from 35% to 65% among patients with cutaneous lesions. Mortality rates of EM are not well documented. The literature does suggest however that 5% of SJS to 30% of TEN may be fatal.[13]

ETIOLOGY AND PATHOGENESIS

EM arises as a consequence of immune-complex mechanisms involving antigen-antibody reactions that target small blood vessels in the skin or mucosa. In approximately 90% of cases, the precipitating event relates to infection, with the herpes

Table 1
Summary of epidemiologic studies of erythema multiforme reporting the global incidence rates

Study	Study Duration	Location	Annual Incidence Rate of EM Group Requiring Hospitalization per 1 Million
Chan et al,[33] 1990	1972–1986	Washington	4.2
Kamaliah et al,[34] 1998	1987–1994	Malaysia	2.1
Schöpf et al,[35] 1991	1981–85	Germany	1.01
Strom et al,[36] 1991	1980–1984	3 US states	39.9
Farthing et al,[28] 1995	—	England	5/10
Roujeau & Stern,[37] 1994	—	Sweden	0.4–6
Forman et al,[38] 2002	1985–1995	Ontario, Canada	6
Mittmann et al,[39] 2004	1995–2000	Canada	1.5
Sanchis et al,[40] 2010	—	Spain	0.8–6

simplex virus playing a predominant role in 70% to 80% of cases.[14] Other precipitating or triggering factors may include medications, especially sulfonamides, nonsteroidal anti-inflammatories, penicillins, and anticonvulsants. Although less common, genetic factors, neoplastic conditions (renal and gastric carcinoma), autoimmune disease (inflammatory bowel disease), radiation, and food additives/chemicals have also been reported.[15,16] Certain human leukocyte antigen (HLA) phenotypes, such as HLA 36 and HLA 35 may predispose patients to develop recurrent EM in response to a range of stimuli.[17–19] The summary of etiologic associations with EM is presented in **Table 2**.

Table 2
Etiologic factors for developing erythema multiforme

Infections Approximately in 90% of cases	Viral in descending order of incidence	Herpes viruses; HSV-1 and HSV-2, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus
		Adenoviruses
		Enteroviruses; coxsackie virus B5, echoviruses
	Bacterial in descending order of incidence	*Mycoplasma pneumoniae*
		Corynebacterium diphtheriae
		Hemolytic streptococci
		Legionella pneumophila
		Salmonella
		Mycobacterium leprae
		Pneumococcus
Drugs (less than 10% of cases)	Highly suspected in descending order of incidence	Sulfonamides (trimethoprim, sulfamethoxazole)
		Nonsteroidal anti-inflammatory drugs
		Penicillins
		Anticonvulsants (barbiturates, carbamazepine)
		Hydantoids
		Valproic acid
		Allopurinol
		Antifungal (Terbinafine)
		Oxicam[a] (piroxicam, tenoxicam)
	Others	Imidazole
		Chlormezanone
		Systemic corticosteroids
		Cephalosporins
		Quinolones
		Tetracycline
Immune condition	Immune disease	Graft versus host disease
		Inflammatory bowel disease
		Polyarteritis nodosa
		Sarcoidosis
		Systemic lupus erythematous
	Immunization	Bacille Calmette-Guérin, hepatitis B and smallpox immunization
Others	Food additives	Benzoates
		Nitrobenzene
	Chemicals	Perfume
		Terpenes

[a] Members of a class of nonsteroidal anti-inflammatory drugs that bind closely to plasma proteins.

The most common trigger for the development of EM is the herpes simplex virus (HSV-1 and HSV-2).[4,14] This association is supported by the detection of HSV DNA in 60% of patients clinically diagnosed with recurrent herpes-associated EM (HAEM) and in 50% of patients with recurrent idiopathic EM using polymerase chain reaction (PCR) of skin biopsy specimens.[18] In most cases of cutaneous EM, HSV-1 had a predominant role with reported prevalence of HSV-1 in 66.7% of cases, HSV-2 in 27.8% of cases, and with both HSV types in 5.6% of cases.[20]

The pathogenesis pathway of EM has been based on investigative studies of HAEM. It has been suggested that an autoreactive T-cell trigger by viral antigen-positive cells containing the HSV-DNA polymerase gene play an important role.[21] EM is initiated by the expression of HSV-DNA fragments that are transported and generated by peripheral blood mononuclear cells (PBMCs), principally macrophages and CD34+ Langerhans cell (LC) precursors, presumably by the vascular route. Inflammatory responses are initiated by viral gene expression in the skin and the recruitment of HSV-specific CD4+ T-helper 1 (Th1) cells. Interferon gamma (IFN-γ) generated by this response upregulates cytokines and chemokines that amplify cutaneous inflammatory events both with increased sequestration of circulating leukocytes, monocytes, and natural killer (NK) cells and with the recruitment of autoreactive T-cells to the epidermis (**Figs. 1** and **2**).[21] The mechanism of autoreactive T-cell generation is still unclear. The outcome is epidermal damage resulting from lysis of surrounding keratinocytes, release of various cytotoxic factors, keratinocyte growth arrest, and apoptosis. The HSV-DNA polymerase gene is located in the basal keratinocyte and lower spinous cell layers.[22,23] In contrast to viral-associated EM, drug-induced erythema multiforme is associated with tumor necrosis factor-α (TNF-α), perforin, and granzyme B, which cause the epidermal destruction seen in the disease with involvement of CD8+

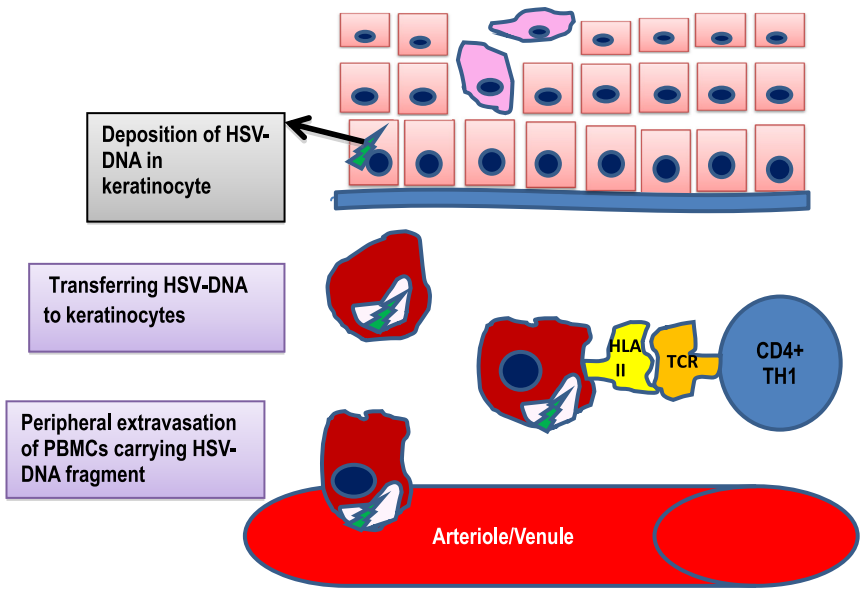

Fig. 1. Seven to 21 days after primary or recurrent viral infection, circulating PBMCs, macrophages, and CD34+ Langerhans cells engulf HSV-DNA, and migrate to epidermis to transfer this antigen to keratinocytes. It has been suggested that HSV-DNA fragments in circulating or decaying PBMCs are released at the time of PBMC deposition on the skin.

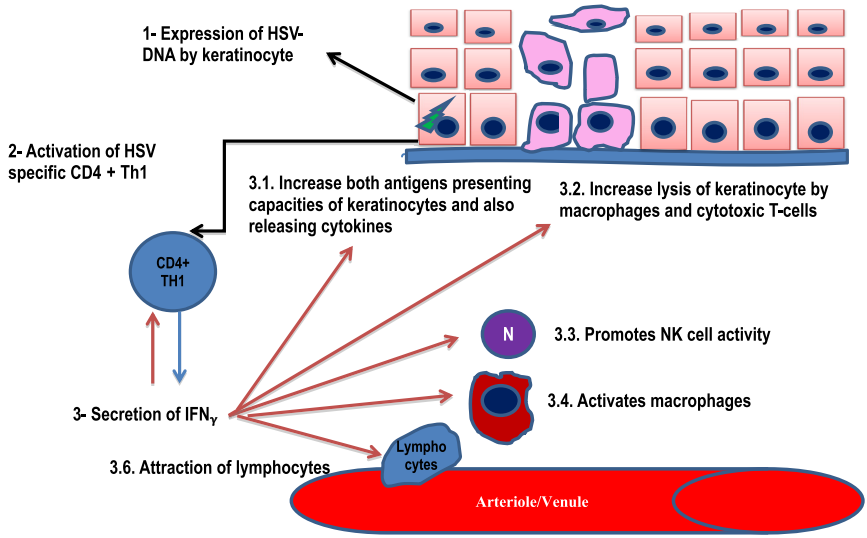

Fig. 2. Expression of HSV DNA in keratinocytes leads to activation of HSV-specific CD4+ Th1 cells, which produces interferon γ. Epidermal cell damage results from attacks by cytotoxic T-cells, NK cells, and monocytes.

T-cell attacks.[21] A summary of clinical and histopathological features of HAEM and drug-induced EM is presented in **Table 3**.

CLINICAL PRESENTATION

The term EM was coined to reflect the multiple and varied clinical appearances that are associated with this condition. The clinical behavior of EM can be divided into

Table 3
Clinical and histopathological difference between HAEM and drug-induced EM

	HAEM	Drug Induced EM
Etiology	HSV-1, HSV-2	Drugs
Clinical features	No or mild prodromal signs/ symptoms; acute; self-limiting; recurrent	Flu-like prodrome, acute, self-limiting, not recurrent
Predilection site	Skin: acral extremities, target lesions Mucosal lesions are absent/and oral lesions are minimal	Skin: acral extremities, blisters Mucosal lesions (in most cases oral mucosa): prominent
Histopathology	Focal keratinocyte necrosis; edema; predominant mononuclear infiltration: CD4+	Extensive keratinocyte necrosis; less edema; predominant mononuclear infiltration: CD4+
Immunochemistry	Positive for HSV DNA-PCR and interferon γ	Negative for HSV DNA PCR; positive for tumor necrosis factor α
Mortality	Not reported	5%–15%

Abbreviations: EM, erythema multiforme; HAEM, herpes-associated erythema multiforme; HSV, herpes simplex virus; PCR, polymerase chain reaction.

3 major subgroups that include classical erythema multiforme, recurrent erythema multiforme, and persistent erythema multiforme.[24] The frequent occurrence of EM over a period of years is known as recurrent erythema multiforme.[25] Persistent EM is a rare condition characterized by the continuous occurrence of typical and atypical lesions without interruption.[26,27] With classic and recurrent disease, there may be prodromal symptoms that precede the eruption of lesions. Young adults are most commonly affected and there can be seasonal clustering in the spring or fall.[28] When HSV is the triggering factor, EM (minor or major) lesions typically begin 10 to 14 days following a recurrent HSV infection (lip most commonly involved).[29]

CUTANEOUS FEATURES

Rarely, there may be prodromal symptoms (ie, fever, malaise, headache, cough, rhinitis, sore throat, myalgia, arthralgia, nausea) associated with erythema multiforme, which typically occur 7 to 14 days before cutaneous lesion development. The classic skin lesion of EM is a target or iris lesion (**Fig. 3**) characterized by concentric erythematous rings separated by rings of near normal color with lesion size ranging from 2 to 20 mm.[4] Typically, there is a symmetric distribution of lesions over the extremities (dorsal surfaces of hands, feet, elbows, and knees). The lesions are usually asymptomatic, although burning or itching sensations have been reported. Less common skin manifestations of EM include macules, papules, vesicles, bullae, and urticarial plaques. Complete recovery from an EM attack typically occurs within 1 to 4 weeks. No scarring occurs. Transient hypopigmentation or hyperpigmentation may be seen.[4]

ORAL MANIFESTATIONS

Oral mucosal lesions occur in more than 70% of EM cases. EM may also present as oral mucosal ulcerations with few or no skin lesions.[30] There may be considerable variability in the appearance of oral lesions, ranging from diffuse oral erythema to multifocal superficial ulcerations. Initially, vesicles or bullae may also be present. Any area of the mouth may be involved, with the buccal mucosa, palate, and tongue being most frequently affected. In most cases, lip lesions are observed that show hemorrhagic crusting of the lips (**Fig. 4**). There may be mild to severe oral and perioral pain that may compromise speech, eating, and fluid intake. Lip and oral lesions heal without scarring.[4]

A summary of the similarities and differences between EM, as well as SJS/TEN is presented in **Table 4**.

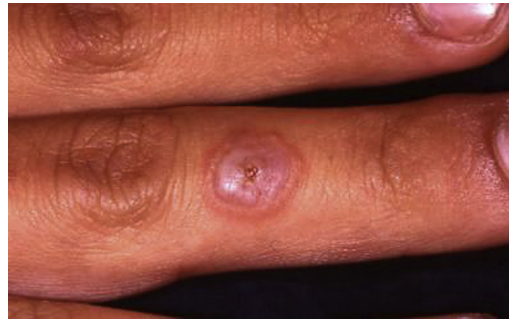

Fig. 3. Target lesions characteristic of EM. (*Courtesy of* Thomas P. Sollecito, DMD, FDS, RCS, Philadelphia, Pennsylvania.)

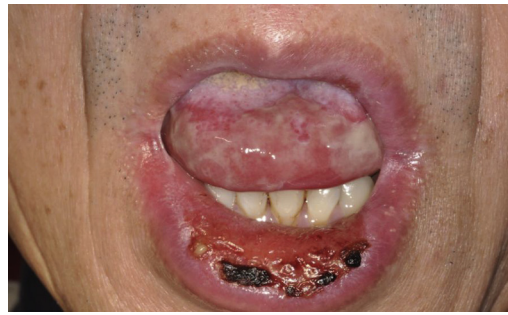

Fig. 4. Hemorrhagic crusting of the lips with tongue ulceration in EM.

HISTOPATHOLOGICAL FEATURES

The histologic feature of peri-lesional tissue in erythema multiforme reveals some characteristic features but none that are pathognomonic of the disease. The histologic features are variable and this is reflective of the wide spectrum of clinical presentations. Some features consistently observed include intercellular and intracellular edema of the overlying epithelium, focal microvesicle formation, keratin mucopolysaccharide dystrophy, pooling of an eosinophilic amorphous coagulum within the epithelium, and infiltration of mononuclear and polymorphonuclear cells into all epithelial layers (**Figs. 5** and **6**). There may also be acanthosis and elongation of rete pegs, generalized diffuse infiltrate of mixed mononuclear cells of the upper portion of the lamina propria, and vasodilation of blood vessels with marked connective tissue edema causing large zone separation at the basement membrane level.[3] Immunofluorescence testing reveals that deep perivasculitis is positive for immunoglobulin M and C3.[31]

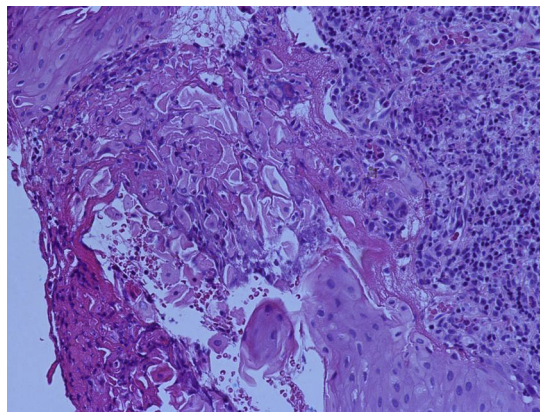

Fig. 5. Histopathology (hematoxylin-eosin [H&E] staining, magnification $\times$10) of EM (buccal mucosa). Intercellular and intracellular edema of the overlying epithelium, focal microvesicle formation, keratin mucopolysaccharide dystrophy, pooling of an eosinophilic amorphous coagulum within the epithelium, and infiltration of mononuclear and polymorphonuclear cells into all epithelial layers.

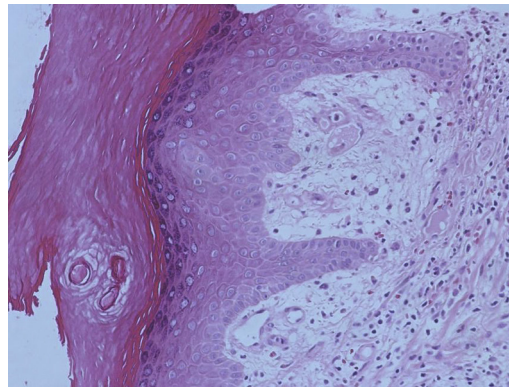

Fig. 6. Histopathology (H&E staining, magnification ×10) of EM (skin of finger). Acanthosis and elongation of rete pegs, generalized diffuse infiltrate of mixed mononuclear cells of the upper portion of the lamina propria, and vasodilation of blood vessels with marked connective tissue edema.

DIAGNOSTIC TECHNIQUES AND EVALUATION OF EM

The diagnosis of EM is mainly based on the history and clinical presentation, as histopathologic features and laboratory investigations are nonspecific. Typically, the history includes acute onset of oral and/or skin lesions, possibly preceded by an HSV infection or a history of recent drug intake. This history, combined with characteristic target lesions of the skin and mucous membranes, supports the diagnosis of EM. Direct and indirect immunofluorescence may help in distinguishing EM from other types of vesiculo-bullous lesions. On an individual case basis, a Tzanck smear, swab for HSV-PCR, or other serologic investigations may be helpful in ruling out an inflammatory, autoimmune, or malignant disorder.

DIFFERENTIAL DIAGNOSIS

The patient history and clinical presentation should provide the most pertinent information in making a diagnosis of EM. However, other conditions considered in the differential diagnosis are primary HSV gingivostomatitis, autoimmune vesiculobullous diseases, such as pemphigus vulgaris, bullous pemphigoid or paraneoplastic pemphigus, urticaria, SJS, or a fixed drug eruption. The distinguishing features between different types of vesiculobullous lesions are described in **Table 5**.

TREATMENT

Treatment of EM varies according to disease severity. The clinical course of an episode of EM is variable. Complete healing of lesions may take up to 3 to 6 weeks and the disease may recur.

Identification and Treatment of Precipitating Factors

No treatment has been identified that predictably alters the clinical course of EM. HSV-induced EM occurs an average of 8 days after the development of HSV infection, at a time when treatment solely for HSV infection is no longer indicated. In general, treatment should be instituted as appropriate for management of an active viral infection. Any drug suspected to have precipitated EM should be promptly discontinued.

Table 4
Clinical features of EM subgroups, and SJS and TEN

	Site of Involvement	Etiology	Clinical Manifestations	Demographic	Prodromal Signs
EM Minor	Skin • Less than 10% of BSA Mucosa • Uncommon • Most commonly oral mucosa; vermilion border, lip mucosa, gingiva and palate Note: Occasionally EM minor is isolated to the oral mucosa without skin involvement	Infectious in origin	Skin • Symmetric distribution • Predilection for the extensor surfaces of the extremities • Circular asymptomatic erythematous plaques in a concentric array 2–20 mm in size • Negative Nikolsky's sign • Transient hypo or hyperpigmentation at lesion sites Mucosa • Painful, hemorrhagic, superficial ulcerations • Heal without scar Note: complete recovery in 1–4 wk	Young adult (20–40 y) Slightly more in women than men	Rare
EM Major	Skin • Less than 10% of BSA Mucosa $\geq$2 different mucosal site • Most common site is oral mucosa followed by buccal/labial mucosa • Less frequently the floor of the mouth, palate and gingival are involved	Infectious in origin	Skin • Symmetric distribution • Predilection for the extensor surfaces of the extremities • Circular asymptomatic erythematous plaques in a concentric • Negative Nikolsky's sign Mucosa • Larger than EM minor • Heal without scarring • Multiple painful papules, vesicles and widespread ulcerations Note: complete recovery in 1–6 wk	Young adult (20–40 y)	Usually absent but in some patients mild systemic symptom such as fever or chills

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Table 4
(*continued*)

	Site of Involvement	Etiology	Clinical Manifestations	Demographic	Prodromal Signs
SJS	Skin • Less than 10% of BSA Mucosa ≥2 different mucosal sites (oral mucosal lesions always) • Sudden onset erosion of oral, genital and/or conjunctival mucosa • Buccal mucosa, palate and vermillion border of lip • Oral lesion sometimes precede skin involvement	Drugs	Skin • Atypical flat target-initially a macular, morbilliform rash on the face, neck, chin, and central trunk • Widespread blistering-positive Nikolsky's sign • Scarring may occur Mucosa • Painful extensive irregular hemorrhagic erosions with greyish-white pseudomembranes • Hemorrhagic crusts on lip Note: complete recovery in 2–6 wk	Children ≥15 y; adults Male/Asian	Fever, pharyngitis, headache, myalgia, arthralgia (flulike symptoms)
SJS/TEN	Skin • 10%–30% of BSA Mucosa • Same as SJS	Drugs	• Same as SJS • Always with systemic symptoms	Same as SJS	Flulike symptoms
TEN	Skin • >30% of BSA Mucosa • Severe involvement of many mucosal surfaces, including oral mucosa	Drugs	Skin • Widespread purpuric macules or flat atypical target, widespread erythema and epidermal necrolysis • Bulbar conjunctiva • Positive Nikolsky's sign • Scarring Mucosa • Painful crusts and erosions • Swelling of tongue Note: variable recovery rate; hospitalization required; poor prognosis; mortality 30%–40%	Older adults Female/regional differences	Severe sudden-onset flulike symptoms

Abbreviations: BSA, body surface area; EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 5
Description of typical clinical features and distinguishing features to differentiate erythema multiforme from other vesiculo-bullous lesions

	Clinical Features	Distinguishing Features
Primary herpetic gingivostomatitis	Usually seen among children under 5 y of age; present with multiple painful oral ulcers preceded by vesicles; fever and general malaise	Multiple punctuate ulcerations that coalesce to form larger irregular painful ulcerations; mainly in children; and do not usually present with skin rash
Pemphigus vulgaris	Multiple shallow irregular and painful ulcers proceeded by vesicles or bullae; occurs in middle age; positive Nikolsky's sign; presents as a chronic disease with periods of remission or exacerbation; cutaneous and oral lesions may be seen	EM is acute with target lesions; no presence of antibodies against desmoglein in EM; direct immunofluorescence shows "fish-net" appearance
Bullous pemphigoid	Chronic condition; presents with large bullae or vesicles intraorally; ocular and other mucous membranes may be involved; histologically, a suprabasilar split separating the epithelium and the connective tissue is seen	EM is acute with target lesions; no antibodies detected with immunofluorescence
Paraneoplastic pemphigus	Chronic disease that has polymorphous progressive skin lesions; severe mucosal involvement; presence of underlying malignancy; conjunctiva involvement	EM is acute; not usually associated with malignancy; immunofluorescence microscopy does not show any cell-surface IgG deposition or combined cell surface and basement membrane zone IgG and C3 deposition
Urticaria	Transient plaques with central zone of normal skin or erythema; may have associated mucosal edema	Lack of the central zone typically seen in EM; individual lesions tend to last no more than 24 h
Fixed drug eruption	Single or multiple erythematous plaques with or without central necrosis; less mucosal involvement	The medication history typically reveals temporal trends of oral lesions associated with medication

Abbreviations: EM, erythema multiforme; Ig, immunoglobulin.

Treatment of Mild EM

Treatment of mild disease (limited oral and cutaneous involvement), should be focused on symptomatic relief using topical anti-inflammatory, anesthetic, or analgesic agents. Some of the drugs that can be used are as follows:

- Fluocinonide 0.05% or other topical steroid agents need to be applied to involved areas 2 to 3 times per day
- Mouthwash containing equal parts of viscous lidocaine 2%, diphenhydramine (12.5 mg/5 mL), and an aluminum hydroxide and magnesium hydroxide mixture (Maalox) as a swish-and-spit, up to 4 times per day.

Treatment of Severe EM

In the severe form of EM, there may be extensive lesions and inability to ingest foods. Systemic steroids may be advised in consultation with a physician depending on the etiology and severity of disease. The most commonly used steroid is prednisone 40 to 60 mg per day, which is tapered over 2 to 4 weeks. However, in some cases, systemic steroid use only partially suppresses disease activity and may increase the risk of disease chronicity and prolonged duration of attacks.[32]

Recurrence and Supportive Care

Depending on the case, recurrence of EM should be avoided by providing antiviral therapy or immunosuppressive therapy. Continuous antiviral therapy is effective for the prevention of recurrent HSV-associated EM. A 6-month trial of either acyclovir (400 mg twice daily), valacyclovir (500 mg twice daily), or famciclovir (250 mg twice daily) has been suggested. Supportive care should be provided in the form of a liquid diet, intravenous fluids, electrolytes, and nutritional support.

Other Treatments

Other recommended treatment for patients with severe recurrent EM who fail to respond to continuous systemic antiviral therapy are azathioprine (100 to 150 mg/d or 2 mg/kg/d in patients with normal thiopurine methyltransferase activity), mycophenolate mofetil (1000 mg twice daily), or dapsone (100 to 200 mg/d). Data regarding the usefulness of these medications are limited.

SUMMARY

EM is a widespread hypersensitivity reaction that occurs with varying degrees of severity. HSV infection is the most common precipitator of EM, and the possibility of HSV-induced disease should be considered in all patients. The history of lesion eruption and related clinical findings provides the most important information for the diagnosis of EM. Patients should be queried regarding prodromal symptoms as well as recent introduction of any new medications. The clinical course of EM is usually self-limiting, resolving within weeks without significant sequelae. However, in a minority of cases, the disease recurs frequently over the course of years. Most patients with EM can be managed with symptomatic therapy alone. However, patients with severe EM may require hospitalization for hydration, analgesia, antiviral therapy, and systemic steroids.

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