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Erythema multiforme: a review and contrast from Stevens-Johnson syndrome/toxic epidermal necrolysis

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Erythema multiforme (EM) is a typically mild, self-limiting, and recurring mucocutaneous reaction characterized by target or iris lesions of the skin and mucous membranes. It is most often a recurring phenomenon with great variability (weeks to years) in the interval between episodes. It is much more common in persons under 40 years of age and is rarely seen under the age of 3 years or over the age of 50 years. There is little gender difference, and no ethnic or geographical predominance has been identified [1]. There can be seasonal clustering in the spring [2,3]. In contrast, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are less common and more severe conditions that typically occur in adults. SJS and TEN are usually a single event caused by a drug exposure. Women are affected twice as often as men [4]. There is no ethnic predominance, but there may be a hereditary component to this condition [5]. There is an increased incidence of SJS and TEN in the HIV-infected population [6].

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Historically EM comprised a disease spectrum that is often classified based on increasing degrees of disease severity. The spectrum included a mild or minor form, EM, and a more severe or major form, SJS. Completing the spectrum was the most severe form of the disease, TEN or Lyell's syndrome [7]. The clinical features that unified these diseases under the label of EM are the target or iris lesion, similar mucosal features, and the common pathologic finding of epidermal necrosis. The common pathogenesis of cytotoxic immunologic attack against exogenous antigens on the keratinocytes further unified these entities.

There is now evidence suggesting that EM, SJS, and TEN are not a continuum of the same immune disorder. SJS and TEN are probably the same disease, differing only in the area of involvement and the severity of systemic findings [8]. EM and SJS/TEN differ in their cause, clinical presentation, pathology, and therapy [1,9,10]. This article focuses on EM. The similarities and differences between EM and SJS/TEN also are discussed.

Etiology

EM is almost always infectious in origin; herpes simplex virus (HSV) is the infectious agent in 70% to 80% of cases [11]. HSV-1 and HSV-2 are known to trigger EM. There is no documented association between EM and varicella zoster virus. HSV antigens are difficult to culture and are difficult to observe by the electron microscope in lesions of EM. HSV antigens, however, are expressed on the endothelial cells of the blood vessels and keratinocytes of EM lesions, which are the target of the immune attack. These fragments of HSV DNA are detected in lesions by in situ hybridization and by polymerase chain reaction. HSV DNA can be found in the peripheral blood in acute episodes and in EM lesional sites up to 3 months later [12]. In the acute phase, circulating mononuclear cells contain HSV DNA in more than 60% of cases. The prophylactic use of acyclovir to prevent the recurrence of EM, even in individuals with no clinical evidence of HSV infection, supports the pathogenic relevance of this virus [13]. Other viruses and progesterone therapy have occasionally been documented as triggers of EM. The evidence is not compelling in these situations. In fact, it has been suggested that they are simply imitators of EM.

In contrast to EM, drugs precipitate 80% to 95% of the cases of TEN and more than 50% of cases of SJS [14]. These drugs are all forms of sulfonamides; in descending order of incidence they are trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory agents, penicillins, anti-convulsants such as barbiturates and carbamazepine, hydantoins, valproic acid, allopurinol, and terbinafine [14,15]. In total case reports have implicated 100 different drugs. Presumably, the cytotoxic T-cell response is against keratinocytes expressing drug antigens. The remaining 10% of cases may be caused by infections, such as mycoplasma pneumonia, by vaccination, or by graft-versus-host disease. The condition is idiopathic in a small fraction of cases [16].

Pathology

The pathology of EM differs from that of SJS/TEN. In EM there is a perivascular infiltrate of CD4 and CD8 lymphocytes surrounding swollen blood vessels in the upper dermis with papillary dermal edema and vacuolar degeneration of the basal layer, subdermal blister formation, and epidermal necrosis of keratinocytes that increases with older lesions. The individual necrotic keratinocytes are surrounded by CD8 cells, termed ''satellite cell necrosis.'' In most cases the attack is against HSV-DNA particles expressed on the blood vessels and keratinocytes. In the epidermis of EM there is an overproduction of interferon γ (IFN-γ) by CD4+ T helper-1 cells [17]. IFN-γ is not found in the drug-induced condition [18].

SJS/TEN exhibits much more widespread necrosis of the epidermis and little vascular inflammation of the dermis. Presumably the drug antigens are expressed only on the keratinocytes, not the blood vessels. In fact, there is a remarkable absence of significant lymphocytes around the vessels, and few are seen in the epidermis.

TEN, especially, shows a lack of inflammatory cells but a predominance of macrophages and dendrocytes in the dermis and epidermis with a much greater overproduction of tumor necrosis factor-α (TNF-α) in the epidermis than in EM [19]. In EM the predominant cytokine is IFN-γ. The source of the TNF-α is both from macrophages and keratinocytes. The basal cell necrosis is widespread, causing extensive subepidermal separation. In severe cases, fibrinoid necrosis may occur in internal organs such as the trachea and bronchi, intestines, spleen, and kidneys.

Clinical presentation

The clinical appearance of cutaneous EM differs from that of SJS/TEN. EM is characterized by multiple target or iris lesions (Fig. 1). All lesions typically present within approximately 3 days of onset. There may be hundreds of lesions, but less than 10% of the body surface area is usually involved. The lesions are in a fixed position with a symmetric distribution. They present as circular erythematous plaques in a concentric array with lesion size ranging from 2 to 20 mm. A central blister or area of necrosis may be present. Initially the lesions are seen acrally (dorsal surfaces of hands, feet, elbows, and knees). The face may also be involved. Less commonly, lesions may also be seen on the palms, soles, thighs, and buttocks. Lesions may appear at sites of trauma or physical irritation and at sites of sun exposure. Prodromal symptoms are rare, and few systemic symptoms are present during the EM episode. When present, symptoms are typically mild and nonspecific (cough, rhinitis, low-grade fever, malaise, diarrhea, myalgia, and arthritis). The lesions are usually asymptomatic, although burning or itching sensations have occasionally been reported. Complete recovery from an individual EM attack ranges from 1 to 4 weeks,

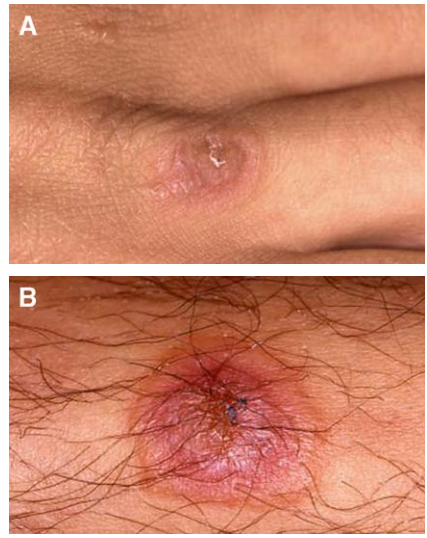

Fig. 1. Target or iris lesions on the dorsal surface of the (*A*) hand and (*B*) leg in a patient with erythema multiforme.

with individual lesions typically resolving in 10 to 14 days. Transient hypo- or hyperpigmentation may be seen at lesion sites in some cases. There are no other sequelae [3]. EM is a recurrent phenomenon with highly variable frequency and severity of episodes. It does not progress to SJS/TEN.

Oral mucosal lesions occur in more than 70% of cases of EM. Although less well recognized, EM does present as oral mucosal ulcerations with few or no skin lesions (Fig. 2) [20]. Preferred sites of involvement include the lips, alveolar mucosa, and palate. Lip involvement is almost universal (Fig. 3). Although target or iris lesions may be seen, superficial ulcerations or crusted lesions are more common. An episode of recurrent HSV may precede the lesions of EM; the average interval between the onset of an episode of recurrent HSV and EM is 8 days (range, 2–17 days). Despite this interval, it may be difficult to distinguish the initial herpes labialis lesion and the lip lesions of EM (Fig. 4). Not all episodes of EM are preceded by a clinically identifiable episode of HSV infection. Also, EM does not predictably follow an episode of recurrent HSV infection [3]. Unlike the skin lesions described, oral lesions are frequently painful and may compromise speech and eating. These lesions heal without scarring. Medical complications related to EM are uncommon.

With SJS/TEN there is considerable variability in the interval between exposure to the offending agent and onset of skin eruptions, severity of symptoms, surface area and region of involvement, and associated constitutional symptoms. SJS/TEN may occur within 45 days of a drug treatment being started or within a few days after repeat exposure. In many

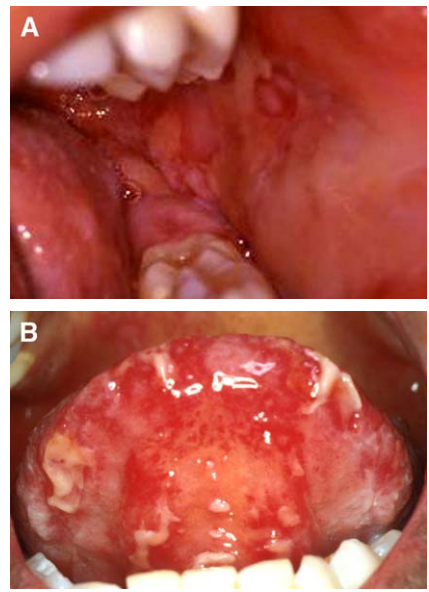

Fig. 2. Oral mucosal lesions of erythema multiforme.

patients a nonspecific prodrome occurs 7 to14 days in advance of lesion development. Symptoms may include fever, malaise, headache, cough, rhinitis, sore throat, myalgia, arthralgia, nausea, and vomiting. Initially a macular, morbilliform rash develops on the face, neck, chin, and central trunk making the presenting appearance and distribution of the lesion different from that seen in EM. In SJS/TEN lesions spread rapidly over much of the body. Target lesions are seen but are larger and less well defined than in EM. The lesions tend to coalesce. The skin is tender, and some lesions exhibit the Nikolsky sign. Large areas of fragile skin involving more than 30% of the body surface define TEN. Many mucosal surfaces are severely affected. The lips, buccal mucosa, and palate may be involved (Fig. 5). Sometimes the extensive hemorrhagic sloughing tissue extends to the whole oral cavity, larynx, esophagus, and respiratory tree (Fig. 6). The bulbar conjunctiva can

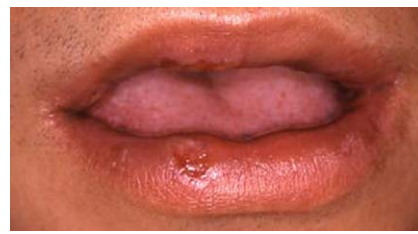

Fig. 3. Lip lesion of erythema multiforme.

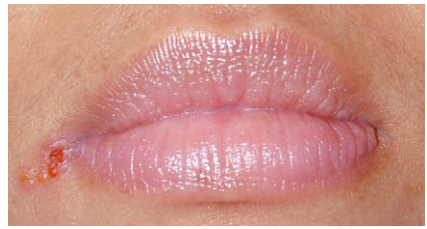

Fig. 4. Recurrent lesion of herpes labialis.

be involved, and sometimes corneal ulceration and uveitis develop. Late scarring of the conjunctiva and corneal ulcerations can result in blindness. Genital ulcerations can develop leading to urinary retention and phimosis. Sepsis from widespread skin infection, renal failure, and cardiac complications can lead to death in a significant percentage. In contrast to EM, repeat attacks do not occur if the offending drug is strictly avoided. Re-exposure to the same agent can again precipitate SJS/TEN, often with a more severe clinical course.

Diagnostic techniques

The diagnosis of EM is based on history and the clinical presentation. Laboratory investigations typically reveal no abnormalities of significance.

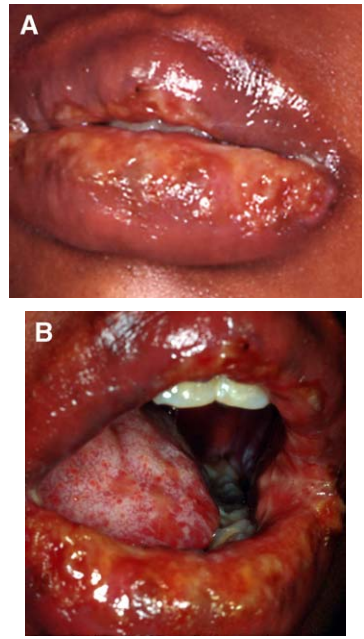

Fig. 5. Lip lesions in a patient with Stevens-Johnson syndrome.

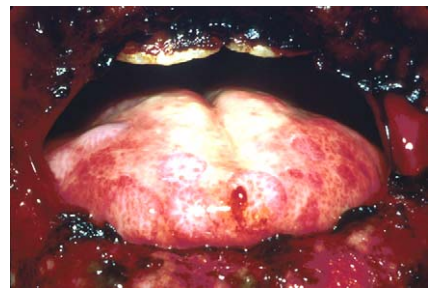

Fig. 6. Lip and oral lesions in a patient with toxic epidermal necrolysis. (Courtesy of Michael Glick, DMD, Newark, NJ.)

In SJS/TEN there is an elevation in the blood sedimentation rate. Moderate leukocytosis, fluid and electrolyte imbalances, microalbuminuria, hyponatremia, elevated liver transaminase, hypoproteinuria, and anemia also may be present. A transient decline in CD4+ T-lymphocyte counts may also be seen during the acute phase of TEN [21]. Numerous other laboratory abnormalities may also be identified depending on organ involvement or the presence of secondary infection [22].

Treatment options

The differences in cause and in clinical severity between EM and SJS/TEN significantly affect treatment. The mild symptoms associated with EM are typically treated symptomatically. Anti-inflammatory, anesthetic, and topical corticosteroid suspensions provide symptomatic relief of painful oral lesions. The importance of adequate fluid intake should be emphasized. Individuals with EM do not require hospitalization. No treatments have been identified that are known to alter the clinical course. Administration of systemic steroids is controversial and, in some cases, may prolong the condition.

Early treatment of recurrent HSV infection is the recommended approach to prevent recurring attacks of EM. Systemic antiviral agents have abortive or suppressive actions. Abortive treatment uses famciclovir, 125 mg, two times/day for 5 days, or valacyclovir, 500 mg, two times/day for 5 days. Effective therapy depends on initiating treatment during the prodromal phase. For example, a tingling sensation of the lip may herald an attack of herpes labialis. If the drug therapy is started after the herpes labialis lesion appears, EM will not be aborted. When there is no prodrome, suppressive therapy may be tried. Famciclovir, 125 to 250 mg/day, or valacyclovir, 500 to 1000 mg/day for a year, may totally prevent EM attacks. After 1 year attacks may be less severe and frequent or may recur as before. When suppressive treatment does not work, it may indicate a trigger other than HSV. In this case suppressive treatment is a test to determine if HSV or some other trigger

is involved. In the few cases where HSV does not seem to be the trigger, dapsone, hydroxychloroquine, azathioprine, and thalidomide have been advocated [3].

There are no standardized guidelines for treatment of SJS/TEN. Recognition and prompt discontinuation of the offending agent is a priority. Use of all drugs should be stopped as quickly as possible, especially those taken within 8 weeks before the onset of TEN symptoms [23,24]. In SJS, oral intake may be limited, so patients may need to be hospitalized to receive replacement intravenous fluids. Ophthalmologic consultation is imperative. Ocular lubricants and elimination of new lid adhesions should be a priority. Patients with TEN benefit greatly from admission to a burn unit where dressings, fluid and electrolyte replacement, and antibiotics are best administered [25,26]. Otherwise, protein loss, electrolyte imbalance, and infection can result in death up to 60% of cases. It is sometimes difficult to choose an antibiotic to fight secondary infection. The use of systemic steroids is controversial because the steroid may stop the immune reaction against the drug but may favor the infection after the epidermis sloughs. Most argue strongly against the use of systemic steroids. The dosage of systemic steroids, if used, should be in the range of 100 mg prednisone; use of systemic steroids should be discontinued within 48 hours once the disease stops progressing [27]. Unfavorable signs in TEN are advanced age, extensive skin lesions, and neutropenia [28]. It is imperative to counsel the patient about avoiding the responsible drug in all of its forms in the future. In the future, treatments tailor-made to the pathogenesis may be available, such as antibodies against CD95 or FasL, the ligand that results in apoptosis or keratinocytes [29].

Summary

EM and SJS/TEN are distinct entities that lead the clinician to different investigations and management. With EM the investigative focus is on identification of an infectious cause, particularly an HSV. With SJS/TEN the effort is to identify the causative drug. Treatment of EM focuses on prevention of HSV infections. Treatment of SJS/TEN focuses on identifying the drug responsible and indefinite avoidance of any form of the culprit drug.

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