PROMINENT FEATURES AND VARIATIONS IN CLINICAL PRESENTATION OF ERYTHEMA MULTIFORME

Vedrana Bulat, Liborija Lugović and Mima Šitum

University Department of Dermatology and Venereology, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Erythema multiforme (EM) is a heterogeneous syndrome often marked clinically by recurrent episodes of symmetrically distributed round skin lesions that evolve with concentric color changes. The spectrum of EM includes eruptions of typical skin lesions located primarily on the extensor surfaces of extremities (EM minor and EM major) or serious systemic illnesses with erosions on multiple mucosal surfaces along with skin lesions (Stevens-Johnson syndrome, SJS) or confluent areas of epidermal detachment (toxic epidermal necrolysis). Thus, the extent of the disease is quite variable, from typical individual target lesions on the arms or legs without oral lesions, through extensive picture with typical and atypical target lesions on the arms or legs with massive oral involvement and severe general symptoms (SJS). EM usually affects young people and heals within a few weeks, depending on initial involvement. It is considered as a special type of skin reaction to various causative agents such as recurrent herpes simplex virus (HSV) infection, mycoplasma or bacterial infections, rarely drugs, x-rays or sarcoidosis. In many cases, these agents cannot be identified. Therapy includes symptomatic measures for itching and pain, and often prophylactic oral acyclovir for recurrent EM due to HSV. In potentially serious cases, systemic steroids may be appropriately used early in the course to lessen the skin and mucosal damage, but supportive medical care and treatment of secondary infection and other complications are crucial elements of the EM management.

Key words: Erythema multiforme – pathology; Erythema multiforme – etiology; Skin – immunology; Skin – pathology; Herpes simplex – complications

Introduction

Erythema multiforme (EM) refers to an array of heterogeneous clinical illnesses with many possible triggering agents, characterized by symmetric target or iris lesions1-4. Originally, in 1866 Ferdinand von Hebra described “erythema multiforme exudaticum” as a self-limited cutaneous eruption lasting for several weeks, with symmetrically distributed, round, erythematous skin lesions, some of which evolved with concentric color changes, producing iris or target lesions or blisters5. This illness caused few systemic symptoms and resolved without significant sequels, but had a remarkable tendency to recur. Although Hebra’s EM was a relatively specific entity, the use of the term has evolved over the last century, and it is now considered as a syndrome with a spectrum of cutaneous eruptions with many causes. Currently, systemic illnesses with prominent mucosal erosions (as described by Stevens and Johnson) or with detachment of large areas of necrotic epidermis (as described by Lyell) are considered within the spectrum of EM1-8.

In recent years, there have been attempts to subdivide EM for definition of the syndrome according to causative factors and management strategies for the various clinical types1-2. One approach is to separate the classic variety described by Hebra from the more serious types by using the term EM minor for Hebra’s disease and the term EM major for the more atypical and severe ill-
nesses\textsuperscript{5,6}. Another approach is clinical classification of cases as bullous EM, Stevens-Johnson syndrome (SJS), or toxic epidermal necrosis (TEN), based on the types of skin lesions and the extent of the skin surface involved\textsuperscript{7,8}. The nosology of EM can be difficult and confusing since the classic variety of EM may have associated oral erosions, but those with SJS and TEN may have confluent areas of epidermal detachment\textsuperscript{1,2}.

Generally, the clinical diagnostic criteria of EM include acute, self-limited or episodic course of symmetrically distributed, fixed, round erythematous lesions with concentric color changes in some of the skin lesions (target lesions), with a duration of 1 to 6 weeks (from onset to healing) and with compatible histopathology\textsuperscript{5}.

The incidence of EM is unknown but is estimated to be at least 1/10,000 population per year\textsuperscript{1}. It typically affects young healthy adults and occurs sporadically throughout the year. Overall, about one-third of cases are recurrent, but the proportion of recurrent cases may be much higher in EM minor\textsuperscript{1,2}.

Prodromal symptoms, usually those of an upper respiratory illness (fever, malaise, myalgias) may precede the more severe varieties, and are seen in about one-third of cases\textsuperscript{1}. EM manifests as typical symmetric skin lesions on the extremities, with a propensity to occur first on the hands and feet, including the palms and soles, and the extensor aspects of the arms and legs\textsuperscript{1,2,10}. The primary lesion is a small round erythematous papule, which may enlarge and coalesce to produce small plaques, or forming concentric zones of color to yield annular lesions, resembling a target or iris (Fig. 1). The outer zones of target lesions are rings of erythema or edema with central portion of an opaque white, yellow or grey (dusky) color. Fluid may accumulate in the center of the lesion, forming a blister, which ruptures easily, producing erosions or crusted lesions. Sometimes there are atypical skin lesions, particularly those of the more serious varieties (EM major), with poorly demarcated maculopapular skin lesions that may progress to confluent areas of erythema, large bullae, or epidermal sloughing\textsuperscript{1,2}.

The typical spread is from acral areas to more proximal areas and the trunk, with new skin lesions erupting over 3 to 5 days (with the exception of SJS or TEN, where the skin of the trunk may be prominently affected, and progression may occur for days to several weeks). This distribution corresponds to photoeruption, with some of the skin lesions accentuated in the areas exposed to sunlight. There is sometimes the isomorphic phenomenon, especially on top of the hands, where skin lesions often begin at the sites of recent scratches or abrasions\textsuperscript{1,2}.

The frequency of mucosal involvement varies widely with EM type (e.g., according to Huff, in EM minor in 25% to 70% of cases, usually limited to the mouth)\textsuperscript{5}. The severe clinical varieties of EM, e.g., SJS, are marked by extensive mucosal involvement at multiple sites, including the mouth, pharynx, esophagus, upper airways, eyes, genitalia and anus. Patients with EM may be minimally incapacitated by the illness, or extremely ill. Those with typical EM minor may complain of itching, swelling, and tenderness of the hands and feet, and pain, but patients with EM major experience fever, arthralgias, myalgias, prostration, severe pain from mucosal erosions, inability to eat or drink, and productive cough\textsuperscript{1,2}.

While EM minor causes virtually no complications, SJS and TEN include significant complications (keratitis, visual impairment, conjunctival scarring, damage of the upper airways pneumonia, pneumothorax, mediastinal emphysema, etc.). In cases with widespread cutaneous damage (TEN), the prognosis is similar to that of a second-degree burn on a similar cutaneous surface area with possible sepsis, and fluid and electrolyte imbalance. Death may occur in up to 18% of cases of EM with pneumonia and in up to 50% of cases of TEN\textsuperscript{5}.

There are two unusual variations of EM, such as oral EM with oral erosions, without skin lesions but with recurrent attacks (only sometimes associated EM skin lesions), best considered a variation of EM minor. In the second, rare entity, chronic EM, skin lesions enlarge slowly over weeks to months, producing large annular

![Fig. 1. Clinical presentation in a patient with erythema multiforme.](image-url)
lesions with peripheral erythema, edema, and crusting, central hyperpigmentation and scaling, usually on the extremities, sometimes photoaccentuated.

**Etiology**

There appear to be many factors that can cause cutaneous or mucocutaneous eruptions consistent with EM, representing potential antigenic stimuli for the immune system (Table 1)\(^1\). The most common causes are viral infection, mostly oral herpes simplex virus (HSV) but sometimes genital HSV (either type 1 or type 2 HSV)\(^1\). Typically, the patient has had a cold sore on the lips 1-2 weeks before the EM or lip lesions may still be present (DNA from HSV was found in the majority of such cases, even idiopathic cases without a definitive history of a preceding HSV lesion)\(^1\). Recurrences are common\(^2,14\). Other viruses may also be implicated, but by far less often. Skin lesions in herpes-associated EM include papules, target lesions, and blisters. The proportion of EM cases brought on by HSV varies among reports, but is likely greater than 50%.

A second well-documented factor for EM is infection with *Mycoplasma pneumoniae*, especially in children and young adults after respiratory infections\(^15\). This illness is characterized by mucosal erosions and bullous skin lesions, usually diagnosed as SJS or bullous EM. Pulmonary mycoplasmal infections are more often associated with severe forms of EM.

Occasionally, EM is related to streptococcal infections (several weeks after a streptococcal tonsillitis or pharyngitis). Other bacterial infections, deep fungal infections, malignant tumors and some autoimmune disorders (lupus erythematosus, Wegener granulomatosis, polyarteritis nodosa) may also be associated with EM\(^1\).

Recent literature contains a number of reports of EM cases, usually SJS or TEN, brought on by drugs (Tables 1 and 2). Frequently incriminated drugs include sulfonamides, penicillins, anticonvulsants, and nonsteroidal anti-inflammatory drugs, sometimes trimethoprim-sulfamethoxazole combinations, and topical sulfa drugs used on the skin and in the eyes. In most instances, there are eruptions with extensive mucosal erosions, large bullae, confluent erythema, or epidermal detachment, mostly within 2 to 3 weeks after the drug has been taken and is not recurrent unless the drug or a cross-reacting drug is readministered\(^1,2\).

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**Table 1. Precipitating factors and drugs associated with erythema multiforme (modified according to Huff)**

<table>
<thead>
<tr>
<th>Infections and other factors</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infections</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Recurrent herpes simplex</td>
<td>Long-acting sulfonamides</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>Trimethoprim-sulfamethoxazole combinations</td>
</tr>
<tr>
<td>Orf</td>
<td>Sulfadoxine-pyrimethamine combinations</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Penicillins</td>
</tr>
<tr>
<td>Psittacosis</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Mycoplasmal infections – mycoplasmal</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>respiratory infections</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>Diphenylhydantoil</td>
</tr>
<tr>
<td>Streptococcal</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Trimepradione</td>
</tr>
<tr>
<td>Mycobacterial infection – tuberculosis</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td></td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td></td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td></td>
</tr>
<tr>
<td>X-irradiation of tumors</td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td></td>
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<tr>
<td>Autoimmune disorders</td>
<td></td>
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</tbody>
</table>
Pathogenesis

There is a modern concept that EM is a syndrome rather than a single disease\textsuperscript{1-4}. Clinical studies, histopathology, and pathogenetic studies indicate certain antigenic stimuli of immune responses, resulting in tissue damage. Clinical observations have also supported the concept that EM represents a mucocutaneous reaction to certain antigenic stimuli (recurrent HSV infections, mycoplasma infections, drugs)\textsuperscript{1-4}. On the other hand, direct immunofluorescence of lesions demonstrates granular deposits of the C3 complement component and sometimes IgM along the basement membrane zone and in upper dermal blood vessels, suggesting an immune complex-mediated injury. Although low levels of circulating immune complexes can be found in the sera of patients with EM, there is no vasculitis typical of immune complex-mediated vascular injury or vascular injury in other organs\textsuperscript{1-2}.

There is a pathogenetic hypothesis that immune reaction leading to tissue damage is largely a cell-mediated immune response, supported by lymphocytes and monocyte-macrophages with a predominance of T lymphocytes, and HLA-DR expression in the epidermis. In certain instances, however, evidence for pertinent antigens in the skin, such as HSV antigens, has been reported\textsuperscript{12}. Maybe antigens of the precipitating infective agent or drug are located in the skin or mucosa (possibly in the epithelium), stimulating cell-mediated immune response as a homeostatic mechanism to eliminate them. If this were the case, EM would be an appropriate immune reaction rather than an ill-defined “hyper-sensitivity” phenomenon. However, currently there is no explanation how such an antigen might become localized at widespread skin or mucosal sites\textsuperscript{1}.

Viral antigens and even DNA are present in the dermis where they trigger the cell-mediated reaction, although it has not yet been elucidated how they produce such symmetric lesions and more widespread skin loss\textsuperscript{1-2}. In case of the delayed appearance after streptococcal infection, a type IV reaction appears most likely. Others have suggested that the primary damage occurs in the epidermis and that the entire process is designed to eliminate epithelial antigens.

Certain individuals may be more likely to develop EM, possibly due to genetically determined characteristics of their immune responses. Associations of EM with certain HLA have been described\textsuperscript{12}. Some HLA types such as B62 and B35 have been increasingly found in EM patients, however, not those commonly associated with autoimmune diseases.

It is supposed that drug-associated EM syndromes are mediated by an immune reaction to drugs or drug metabolites or by toxic effects of a drug. Thus, some individuals have a genetically determined inability to detoxify certain drug metabolites, leading to the accumulation of toxic metabolites and epithelial necrosis, which is most relevant for TEN\textsuperscript{12}.

Clinical Picture

Generally, EM is characterized by target or iris-shaped, concentric round foci, usually about the size of pennies, with the formation of central blisters and symmetric iris lesions\textsuperscript{16}. Old and new lesions can be found side by side. There is typical involvement of the dorsum of the hands and forearms, sometimes also on the palms and soles, with possible extensive involvement of the entire integument. The mucous membranes adjacent to the skin can also be involved, especially in widespread disease, such as reddened conjunctivae (“teary eyes”), or severe oral erosions (stomatitis) with conspicuous hemorrhagic crusts on the lips. Stomatitis is found particularly in the anterior parts of oral mucosa with erosions, ulcerations and fibrosus coatings. The patients often have halitosis, many times with painful mouth opening. The genital mucous membranes can also be affected. Moderate to severe pruritus is usually present. In the beginning, the patients often complain of malaise, joint pain (especially of large joints), and fever\textsuperscript{16}.

Some groups of authors have attempted to produce classification schemes identifying EM minor and EM majus (or bullous EM), or severe skin reactions (TEN, SJS)\textsuperscript{1,3}. The minor form of EM (classic or Hebra form) is characterized by symmetric target- or iris-shaped lesions almost invariably involving the hands, especially dorsal aspects\textsuperscript{1,3}. Often the patient has had a preceding HSV infection, so that lip involvement is hard to assess. A typical lesion is initially an erythematous macule that enlarges and becomes annular. Within 1-2 days, the lesions are about 1 cm in size with a central area of hemorrhage, necrosis and blistering and peripheral pale cyanotic region, enclosed by an erythematous peripheral band. This combination produces the classic, disease-defining target lesion. The lesions may coalesce, evolve into polycyclic patterns and show central healing\textsuperscript{2}. Trunk involvement is uncommon. Mucosal involvement may occur but typically only the lips are involved. The out-
look in such cases is good with rapid healing but recurrences are common (Table 2).

Most such cases are triggered by HSV, which is supported by identification of HSV markers in the skin of EM patients and amelioration by antiviral therapy, even in the absence of an obvious precursor lesion. Minor or ordinary EM has good prognosis with frequently rapid resolution. In most instances, HSV is responsible and recurrences are likely. When other infections or drugs are responsible, the course is often stormier but the chance of recurrence far less.

The major form is severe EM characterized by acral target lesions, but sometimes with trunk involvement and blisters. The blisters are in the center of target lesions and involve less than 10% of the body surface. All patients have mucosal involvement (the mouth, eyes and genital mucosa). Mycoplasma and HSV are the typical triggers. The prognosis is good and recurrences less common, since they are associated with HSV (Table 2).²³

**Toxic epidermal necrolysis (TEN)** manifests in patients with blisters on greater than 30% body involvement, resulting in the loss of large sheets of skin; it starts as erythematous macules on the trunk that rapidly spread and form blisters (Table 2). Mucosal involvement is uncommon; when present, it is usually minimal. The risk of death is significant if patients are not treated appropriately. TEN begins with a prodromal phase, often related to an underlying viral or bacterial disease, with possible fever, rhinitis, conjunctivitis of dysuria, suggesting initial mucosal involvement. A diffuse macular exanthema appears on the trunk and face, which then spreads to the extensor surfaces of the limbs, which rapidly coalesce, forming large flaccid blisters. Then, large sheets of skin are shed. The Nikolsky sign is strikingly positive. The nature of macular lesions is used to define the two types of TEN. The most common variant is TEN with macules, with atypical target lesions on the trunk, which coalesce as blister, causing widespread denudation. Another less common form of TEN is that associated with large areas of erythema preceding macules. Mucosal changes in TEN are identical to those in SJS and they overlap but may be more severe. The eyelids may often have hemorrhagic blisters while severe conjunctivitis may lead to scarring, symblepharon, and even blindness. The oral and genital mucosa may be similarly affected, interfering with feeding, urination and even defecation. The patients are also seriously ill (fever, somnolence, fluid loss, electrolyte abnormalities, glomerulonephritis, pneumonia, hepatitis, etc). TEN is probably the most deadly skin disease; even with expert nursing care the fatality rate is about 40%. While the skin usually heals with little or no scarring, the hair and nails bear witness to the massive insult.

The relationships between TEN and SJS is one of great controversies but it is universally accepted that SJS is a more severe form of EM. Stevens and Johnson (1922) described two children with conjunctivitis, oral ulcerations and fever, who had a disseminated primarily truncal eruption with dark-red erythematous macules, some of which had a necrotic center (Stevens-Johnson syndrome, SJS). The skin lesions in SJS begin on

<table>
<thead>
<tr>
<th>Type</th>
<th>EM minor</th>
<th>EM major</th>
<th>Stevens-Johnson syndrome (SJS)</th>
<th>Toxic epidermal necrolysis (TEN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Herpes simplex virus</td>
<td>Herpes simplex virus, mycoplasma</td>
<td>Drugs, herpes simplex virus, mycoplasma</td>
<td>Drugs</td>
</tr>
<tr>
<td>Skin</td>
<td>Acral target lesions</td>
<td>Acral target lesions</td>
<td>Truncal erythematous macules, with annular and targetoid lesions, minimal pain, max. intensity: 7-15 days</td>
<td>Truncal erythematous macules, diffuse erythema, desquamation, severe pain, max. intensity: 1-3 days</td>
</tr>
<tr>
<td>Blisters (%)</td>
<td>0</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Mucous membrane involvement</td>
<td>+/-</td>
<td>Severe mucosal involvement</td>
<td>Severe mucosal involvement</td>
<td>Mild (rare) mucosal involvement</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Excellent</td>
<td>Good</td>
<td>Good/excellent</td>
<td>Poor</td>
</tr>
<tr>
<td>Recurrences</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Rare (very rare)</td>
</tr>
</tbody>
</table>

*Table 2. Classification of erythema multiforme (EM) groups (modified according to Braun-Falco et al.²)*
the trunk as erythematous macules that coalesce, sometimes with target lesions and blister formation (less than 10% of the body surface). All patients have mucosal involvement. Drug reactions are the most likely trigger, but HSV and *Mycoplasm*a as well as other more uncommon infections may rarely be involved.

Because of imprecise descriptions, these lesions have become known as target lesions and SJS was equated with EM. As previously explained, this statement is incorrect; EM major and SJS are separate entities, but SJS overlaps with TEN.

**Stevens-Johnson syndrome/toxic epidermal necrolysis** overlap manifests clinically as a connection between these two disorders. Patients have severe SJS but do not meet the criteria for TEN and have a prognosis between the two extremes. The Stevens-Johnson syndrome/toxic epidermal necrolysis overlap is characterized by no target lesions on 10%-30% of the body surface with blisters and mucosal disease (but with trunk involvement).

Mucosal findings are seen in severe EM and SJS, involving the lips, sometimes the tongue, palate and buccal mucosa, forming typically large ulcers or erosions and unstable blisters. The lesions of intraoral HSV are smaller and involve almost only the gingiva and lips. The ulcers may spread to the posterior oral cavity, pharynx, larynx, and even lungs and esophagus. Genital involvement produces painful perianal, penile, scrotal and labial ulcers, while urethral involvement may lead to urinary retention.

Many patients, perhaps as high as 90%, have mild conjunctivitis, sometimes purulent. In the more severe forms, there are conjunctival blisters with symblepharon formation, corneal ulcers and iritis or uveitis. Permanent eye damage may result from corneal lesions or synchiae in about 10% of patients with eye involvement. Rarely, patients have primarily oral and ocular involvement, when the term Fuch's syndrome (Fuchs, 1876) is employed (mostly triggered by HSV).

According to systemic findings, patients with EM minor are generally well, but others tend to be ill with fever, arthralgias and myalgias. Those with oral involvement may have difficulty on eating and drinking. The most feared complication is pulmonary disease, which can involve as many as 30% of patients with EM major and more advanced forms. Pneumonia commonly occurs and may lead to death. Other involvement such as myocardial disease, renal failure, and gastrointestinal tract involvement is quite rare.

**Differential Diagnosis**

Differential diagnosis is lengthy, depending on the disease form (e.g., hand-foot-and-mouth disease, leukocytoclastic vasculitis, pemphigus vulgaris, bullous pemphigoid, dermatitis herpetiformis, etc.). There are no specific laboratory findings that suggest TEN, but electrolytes and renal function should be monitored. Early in the disease, the erythrocyte sedimentation rate may be elevated and complete blood count may show elevated hematocrit as the result of fluid loss.

The histopathology of EM provides one rationale for unifying such unrelated clinical findings. There is a mononuclear cell inflammatory infiltrate beneath the epithelium and around blood vessels, and damage to epithelial cells. Initially, there is a lymphocytic perivascular infiltrate with edema and mild exocytosis of red cells. As the disease progresses, epidermal damage occurs with vacuolar degeneration of the basal layer and necrotic keratinocytes. In more severe cases, the entire epidermis may be necrotic. Subepidermal blisters result from the damage at the basement membrane zone.

The histopathology of TEN provides a rapid way to identify the illness. Biopsy shows full thickness epidermal necrosis with little if any lymphocytic infiltrate in the upper dermis. The dermis simply shows edema and vasodilation (so-called empty dermis). Immunofluorescence studies have not identified any disease-defining antibodies. C3 and IgM may be seen along the basement membrane zone and perivascularly, although it is not specific.

**Therapy**

The management of EM requires determination of the subtype and the most likely etiology before introducing specific therapies. When patients have classic EM minor, especially if the eruption is recurrent, reactivation of HSV is the most likely etiology. In SJS, infective agents such as mycoplasmal infection and drugs should be considered, whereas in TEN drugs are almost always the etiology involved. Generally, approaches to therapy of EM include prevention of the antigenic stimulus that leads to EM, and suppression of the host immune response and immune-mediated tissue damage by conservative supportive or symptomatic measures.

Topical therapy for EM is generally supportive and rarely dramatically effective. Local therapy of EM is not
necessary for mild involvement, but bullae should be treated by evacuation and local disinfection, otherwise a shake mixture is sufficient\textsuperscript{16}. Early, non-eroded target lesions can be treated with topical corticosteroid creams or lotions, wet soaks and then ointments, perhaps with antibacterial agents. Topical application of corticosteroids does not influence the course of the disease significantly\textsuperscript{16}. In the flexural areas, drying measures are often helpful. Oral lesions may be treated with anesthetic gargles or rinses to make eating easier\textsuperscript{1,2}. In contrast, everyone agrees that supportive care is the most important factor in caring for the more severe forms (burn care, including infection prophylaxis, fluid restoration and wound care). Consultation with ophthalmologists and internists is crucial to obtain the best outcome.

In severe cases (major type with mucous membrane involvement), a systemic short-term corticosteroid may be indicated, e.g., prednisone in doses of 60 to 100 mg/day tapered over 14 to 21 days. However, the value of systemic corticosteroid therapy is debatable because the phase of cellular damage is over by the time the symptoms appear, and the subsequent clinical course of the disease represents the repair phase\textsuperscript{16}. Also, corticosteroids predispose the patient to additional infections with possible earlier recurrences of HSV infection. The benefit of the agent in more severe disease forms, especially when administered later in the course, has not been documented and some studies have even indicated worsening. In many cases steroids are not initiated until the illness has been present for several days. Systemic steroid therapy, however, may be appropriately instituted in potentially serious cases that are seen early in the course, especially drug-associated SJS or TEN.

Systemic therapy for EM depends heavily on the suspected trigger and the disease severity\textsuperscript{2}. Perhaps the best example of prevention is the use of oral acyclovir as prophylaxis for recurrent HSV lesions (oral acyclovir, 400 to 800 mg/day, suppresses recurrent EM due to HSV), worthwhile in a patient who has several attacks of EM per year. However, there is no convincing evidence that acyclovir therapy of EM or preceding HSV lesion shortens the course of EM\textsuperscript{1,2}. No treatment is recommended after one episode. Patients with recurrent EM without obvious signs of HSV usually benefit as well from acyclovir prophylaxis, suggesting subclinical HSV as a trigger\textsuperscript{1,2}.

Supportive or symptomatic measures and treatment of complications are an important part of the management of EM\textsuperscript{1,2}. Wet compresses are used for exudative skin lesions, and oral antihistamines and topical anesthetic or coating agents for painful oral erosions. Ophthalmologists often recommend them to reduce ocular inflammation and to retard scarring. Analgesics may be required for severe stomatitis\textsuperscript{16}. Stomatitis may require frequent mouthwashes with lukewarm water, possibly with the addition of an antiseptic. When painful, purulent oral erosion associated with foul breath and cervical lymphadenopathy is present, a 5- to 7-day course of oral erythromycin or penicillin for secondary bacterial infection may be of benefit\textsuperscript{1}.

Serious cases of EM, including SJS or TEN, are treated by intravenous fluids and feedings, antibiotics, respiratory care, narcotic analgesics, and moist dressing. When epithelium over large cutaneous areas is lost, care in a special burn unit, including use of burn dressings and grafts, is indicated\textsuperscript{1}. Therapy of TEN is best described as excellent burn care (temperature control, regulation of fluid balance, and avoidance or prompt treatment of secondary bacterial infections). In addition, the eyes and genital area should be paid special attention, being regularly separated and treated with a neutral ointment to reduce the risk of adhesions. The type of nursing care is the major determinant of survival. Fortunately, in TEN little dermal damage occurs and re-epithelialization is usually prompt with better outlook than the initial dismal clinical picture suggests. The biggest controversy in treating TEN is the use of systemic corticosteroids, as high doses of corticosteroids early in the course drug reaction is intuitively wise and must help. No study has shown clear benefit of systemic corticosteroids and several have shown detrimental effects, presumably because of immunosuppression, which is not desirable in someone without epidermis (the risk of many infections)\textsuperscript{1,2}. Plasma exchange has been reported to be effective and should be considered when EM is believed to be drug-induced, especially in cases of TEN\textsuperscript{1}. General measures including bed-rest and often hospitalization are important. Patients with severe and extensive mucosal involvement should have a liquid or soft diet\textsuperscript{16}.

References


Sažetak

ISTAKNUTA OBILJEŽJA I RAZNOLIKOST KLINIČKE SLIKE ERYTHEMA MULTIFORME

V. Bulat, L. Lugoci‘ i M. Štim

Erythema multiforme (EM) je heterogeni sindrom klinički obilježen čestim opetovanim epizodama simetrično raspoređenih numularnih kožnih promjena koje koncentrično prelaze u promjenu izgleda. Spektar EM uključuje izbijanje znakovitih kožnih promjena previsoko smještenih na ekstenzornim stranama ekstremiteta (EM minor) ili teške sistemске bolesti s erozijama na nekoliko služnica zajedno s promjenama kože (Stevens-Johnsonov sindrom, SJS) ili konfluirajuće areale lamelozne deskađemavi (toksična epidermalna nekroliza, TEN). Opseg bolesti je prilično varijabilan: od tipičnih itisu silnih formacija na gornjim ili donjim ekstremitetima bez promjena na služnici usne šupljine do opsežne kliničke slike s tipičnim i atipičnim itis formacijama na gornjim ili donjim ekstremitetima uz opsežno zahvaćanje služnice usne šupljine i teškim općim simptomima (SJS). EM je znatno češći u mladih ljudi i traje nekoliko tjedana, obično o početnoj zahvaćenosti kože. Smatra se da je EM poseban oblik kožne reakcije na različite uzročne čimbenike, kao što su opetovanja infekcija herpes simplex virusom (HSV), mikoplazma ili bakterijska infekcija, rijetko lijekovi, x-rake ili sarkoidoza. U mnogim slučajevima ovi agensi se ne mogu dokazati. Terapija uključuje simptomatske mjere za ublažavanje svrheža i boli, često profilaktilički peroralno aciklovir za ponavljajuće EM uzrokovane virusom HSV. U potencijalno teškim slučajevima sistemski kortikosteroidi mogu se prilagoditi upotrijebiti u ranoj fazi bolesti radi ublažavanja promjena kože i sluznica, ali potporna njega i suzbijanje sekundarnih infekcija i drugih komplikacija su ključni elementi u liječenju EM.

Ključne riječi: Erythema multiforme – patologija; Erythema multiforme – etiologija; Koža – immunologija; Koža – patologija; Herpes simplex – komplikacije