

Erythema Multiforme

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Background

Erythema multiforme (EM) is an acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers.^[1]

Erythema multiforme may be present within a wide spectrum of severity. Erythema multiforme minor represents a localized eruption of the skin with minimal or no mucosal involvement. The papules evolve into pathognomonic target or iris lesions that appear within a 72-hour period and begin on the extremities (see the following image). Lesions remain in a fixed location for at least 7 days and then begin to heal. An arcuate appearance may be present (see the second image below). Precipitating factors include herpes simplex virus (HSV), Epstein-Barr virus (EBV), and histoplasmosis. Because this condition may be related to a persistent antigenic stimulus, recurrence is the rule rather than the exception, with most affected individuals experiencing 1-2 recurrences per year.



Target lesion of erythema multiforme.



Raised atypical targets and arcuate lesions.

Erythema multiforme major and [Stevens-Johnson syndrome \(SJS\)](#), however, are more severe, potentially life-threatening disorders (see the image below). Lesions of Steven-Johnson syndrome typically begin on the face and trunk. They are flat, atypical lesions, described as irregular purpuric macules with occasional blistering. Most patients also have extensive mucosal involvement. More than 50% of all cases are attributed to medications.



Note extensive sloughing of epidermis. Courtesy of David F. Butler, MD.

Erythema multiforme vs SJS and TENS

Controversy exists in the literature with regard to the clinical definitions of erythema multiforme and Steven-Johnson syndrome and whether they are distinct entities or whether they represent a spectrum of one disease process.^[2, 3, 4, 5, 6, 7]

International collaborators have suggested that erythema multiforme and Steven-Johnson syndrome could be separated as 2 distinct clinical disorders with similar mucosal reactions but different patterns of cutaneous lesions.

The confusion between these 2 separate clinical entities began in 1950, when Thomas coined the terms erythema multiforme minor and erythema multiforme major to describe conditions he encountered. Erythema multiforme minor was applied to patients with the illness originally described by Ferdinand von Hebra as erythema multiforme (acute, self-limited condition with characteristic red papular skin lesions) (1860).^[2] Erythema multiforme major was applied to patients who also displayed oral mucosal involvement, similar to that described by Stevens and Johnson (mucocutaneous disorder; febrile erosive stomatitis, severe conjunctivitis, and disseminated cutaneous eruption) (1922).^[3]

Up to 50% of patients with herpes simplex virus (HSV)-associated erythema multiforme have been found to have oral ulcers. However, this is now recognized as a variant of erythema multiforme, rather than Steven-Johnson syndrome. Erythema multiforme and Steven-Johnson syndrome have different precipitating factors and different clinical patterns and are generally recognized to be separate clinical entities.

Consensus classification

According to a consensus definition, Steven-Johnson syndrome was separated from the erythema multiforme spectrum and added to toxic epidermal necrolysis.^[3] Essentially Steven-Johnson syndrome and toxic epidermal necrolysis (TEN) are considered severity variants of a single entity. The 2 spectra are now divided into the following: (1) erythema multiforme consisting of erythema minor and major and (2) Steven-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN).

The clinical descriptions are as follows:

- Erythema multiforme minor - Typical targets or raised, edematous papules distributed acrally
- Erythema multiforme major - Typical targets or raised, edematous papules distributed acrally with involvement of one or more mucous membranes; epidermal detachment involves less than 10% of total body surface area (TBSA).
- SJS/TEN - Widespread blisters predominant on the trunk and face, presenting with erythematous or pruritic macules and one or more mucous membrane erosions; epidermal detachment is less than 10% TBSA for Steven-Johnson syndrome / toxic epidermal necrolysis and 30% or more for toxic epidermal necrolysis.

Historical information

Stevens-Johnson syndrome was considered an extreme variant of erythema multiforme for many years, whereas [toxic epidermal necrolysis \(TEN\)](#) was considered a different entity. However, in 1993, a group of medical experts proposed a consensus definition and classification of erythema multiforme, Steven-Johnson syndrome, and toxic epidermal necrolysis based on a photographic atlas and extent of body surface area involvement.^[3]

See also [Dermatologic Manifestations of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis](#) and [Oral Manifestations of Drug Reactions](#).

Pathophysiology

The pathophysiology of erythema multiforme (EM) is still not completely understood, but it is probably immunologically mediated and appears to involve a hypersensitivity reaction that can be triggered by a variety of stimuli, particularly

bacterial, viral, or chemical products.

Cell-mediated immunity appears to be responsible for the destruction of epithelial cells. Early in the disease process, the epidermis becomes infiltrated with CD8 T lymphocytes and macrophages, whereas the dermis displays a slight influx of CD4 lymphocytes. These immunologically active cells are not present in sufficient numbers to be directly responsible for epithelial cell death. Instead, they release diffusible cytokines, which mediate the inflammatory reaction and resultant apoptosis of epithelial cells. In some patients, circulating T cells transiently demonstrate (for < 30 d) a T-helper cell type 1 (TH1) cytokine response (interferon [IFN] gamma, tumor necrosis factor [TNF] alpha, interleukin [IL] 2). Results of immunohistochemical analysis have also shown lesion blister fluid to contain TNF, an important proinflammatory cytokine.

Other evidence supports the hypothesis that the disease is the result of cell-mediated immune reactions. Individuals possessing human leukocyte antigen (HLA)-B12 are 3 times more likely to develop this disorder. The classic timing for a primary cell-mediated immune reaction is 9-14 days after the initiation of the offending drug. In recurrent exposure, the reaction occurs within several hours to 1-2 days, which is consistent with the timing of a secondary cell-mediated immune response.

Herpes simplex virus

A major cause of erythema multiforme is the herpes virus (HSV). In fact, recent or recurrent herpes has been reported as the principle risk factor for erythema multiforme.

Herpes-associated erythema multiforme (HAEM) appears to represent the result of a cell-mediated immune reaction associated with HSV antigen.^[8, 9] The immunologic reaction affects HSV-expressing keratinocytes. Cytotoxic effector cells, CD8⁺ T lymphocytes in the epidermis, induce apoptosis of scattered keratinocytes and lead to satellite cell necrosis. Neighboring epidermal cells are HLA-DR positive.

A relationship exists between HLA types A33, B35, B62 (B15), DR4, DQB1*0301, DQ3, and DR53 and recurrent erythema multiforme.^[10] In particular, HLA-DQ3 is especially related to recurrent erythema multiforme and may be a helpful marker for distinguishing HAEM from other cutaneous diseases.^[11]

Drug hypersensitivity

The disease process also often involves an abnormal metabolism of a responsible drug. As noted above, the keratinocyte is the ultimate target of this disease process, with keratinocyte necrosis being the earliest pathologic finding.

Patients frequently display an altered metabolism of the responsible drug, and are considered to be slow acetylators, both genotypically and phenotypically. This means that an increased proportion of drug metabolism is directed toward the alternative pathway of oxidation by the cytochrome P-450 system, resulting in increased production of reactive and potentially toxic metabolites. Affected individuals have a defect in the ability to detoxify these reactive metabolites, which may then behave as haptens by binding covalently to proteins on the surface of epithelial cells. This may then induce the immune response, leading to the severe skin reaction.

Etiology

Many suspected etiologic factors have been reported to cause erythema multiforme (EM). Both erythema multiforme and Steven-Johnson syndrome may be induced by medications, but infectious agents are also considered to be a major cause of erythema multiforme. However, approximately 50% of cases are idiopathic, with no precipitating factor identified.

A previous history of erythema multiforme and male sex has also been reported as risk factors, but pregnancy may contribute to development of erythema multiforme as well.

Postvaccination causes include Bacille Calmette-Guérin (BCG) vaccination, oral polio vaccine, vaccinia, and tetanus/diphtheria.

HSV and other infections

Infectious causes are more common in children and are implicated more commonly in erythema multiforme.

Erythema multiforme minor is regarded as being commonly triggered by herpes simplex virus (HSV) (types 1 and 2), and HSV is the most common cause in young adults; in fact, many instances of idiopathic erythema multiforme minor may be precipitated by subclinical HSV infection. Among other infections, *Mycoplasma* species appear to be a common cause.

Bacterial

Bacterial infections include borreliosis, cat scratch disease, diphtheria, hemolytic streptococci, legionellosis, leprosy, *Neisseria meningitidis*, *Mycobacterium avium*

complex, *M pneumoniae*,^[12, 13] pneumococci, tuberculosis, *Proteus/Pseudomonas/Salmonella/Staphylococcus/Yersinia* species, *Treponema pallidum*,^[14] tularemia, *Vibrio parahaemolyticus*, Vincent disease, and rickettsial infections. Chlamydial infections include lymphogranuloma venereum and psittacosis.

Viral

Viral infections include Adenovirus, coxsackievirus B5, cytomegalovirus (CMV), echoviruses, enterovirus, Epstein-Barr virus (EBV), hepatitis A / B / C viruses (HAV / HBV / HCV), HSV, influenza,^[15] measles, mumps, parvaccinia, parvovirus B19, poliomyelitis, varicella-zoster virus (VZV), and variola.

Virus-drug interactions include CMV infection–terbinafine^[16] and EBV infection–amoxicillin.^[17]

Other

Fungal infections include coccidioidomycosis, dermatophytosis, and histoplasmosis.

Parasitic infections include *Trichomonas* species and *Toxoplasma gondii*.

Drugs

More than 50% of cases are related to medication use, but no test reliably proves the link between a single case and a specific drug.

Regarding medications, sulfa drugs are the most common triggers (30%). A slow acetylator genotype is a risk factor for sulfonamide-induced Steven-Johnson syndrome.^[18]

The second most commonly involved agents are the anticonvulsants, including barbiturates,^[19] carbamazepine,^[19] hydantoin, phenytoin,^[19] and valproic acid. Prophylactic anticonvulsants after surgery for a brain tumor combined with cranial irradiation may result in life-threatening Steven-Johnson syndrome.^[20]

Causative antibiotics include penicillin, ampicillin, tetracyclines, amoxicillin, cefotaxime, cefaclor, cephalixin, ciprofloxacin,^[21] erythromycin, minocycline, sulfonamides, trimethoprim-sulfamethoxazole, and vancomycin.

Antitubercloid agents such as rifampicin, isoniazid, thiacetazone, and pyrazinamide are also known offenders. Antipyretic agents as triggers include analgesics, especially aspirin as well as phenylbutazone, oxyphenbutazone, and phenazone.

Others drugs that may cause erythema multiforme include acarbose, albendazole, allopurinol,^[19] arsenic, bromofluorene, quinine (Chinine), cimetidine, clofibrate, corticosteroids, diclofenac, didanosine, dideoxycytidine, diphosphonate, estrogen, etretinate, fluconazole, griseofulvin,^[22] gabapentin, granulocyte-macrophage colony-stimulating factor (GM-CSF), hydralazine, indapamide, indinavir, lamotrigine,^[19] methazolamide, mefloquine, methotrexate, meprobamate, mercurials, minoxidil, nifedipine, nevirapine,^[19] nitrogen mustard, nystatin, nonsteroidal anti-inflammatory drugs (NSAIDs), phenolphthalein, piroxicam,^[19] pyritinol, progesterone, potassium iodide, sulindac, suramin, saquinavir, thiabendazole, thiouracil, terbinafine, theophylline, vandetanib,^[23] verapamil, and dihydrocodeine phosphate.^[24]

Contact exposure

Contactants include ammoniated mercury, budesonide, bufexamac, capsicum, chloromethylnaphthalene, desoximetasone, dinitrochlorobenzene (DNCB), disperse blue 124, diphenylcyclopropenone, fire sponge (*Tedania ignis*), herbal medicines (eg, *Alpinia galanga*),^[25] isopropyl-*p*-phenylenediamine of rubber, nickel, nitrogen mustard, oxybenzone, phenylbutazone, poison ivy,^[26] proflavin, resin, rosewood, and triamcinolone acetonide.

Other etiologic factors

The following have also been reported as causes of erythema multiforme:

- Flavorings and preservatives, such as benzoic acid and cinnamon^[27]
- Immunologic disorders, such as transient selective C4 deficiency of infancy,^[28] collagen diseases, vasculitides, sarcoidosis, non-Hodgkin lymphoma, leukemia, multiple myeloma, myeloid metaplasia, and polycythemia
- Physical or mechanical factors, such as tattooing, radiotherapy, cold, and sunlight
- Foods, including salmon berries and margarine
- Malignancy
- Hormonal

Epidemiology

The exact incidence of erythema multiforme (EM) in the United States is unknown;

however, as many as 1% of dermatologic outpatient visits are for erythema multiforme. Globally, the frequency of erythema multiforme is estimated at approximately 1.2-6 cases per million individuals per year.

Before the human immunodeficiency virus (HIV) epidemic among young males, there was a slight female predominance of this disease. However, erythema multiforme is currently more common in younger males (male-to-female ratio, range of 3:2 to 2:1) (mainly second to fourth decades, but can include children and adolescents [20%]^[29]). The condition is rare in children younger than 3 years and in adults older than 50 years.

The following medical conditions seem to predispose individuals to a higher risk of developing the disorder: HIV infection, corticosteroid exposure, bone marrow transplant, systemic lupus erythematosus (SLE), graft versus host disease (GVHD), and inflammatory bowel disease (IBD). Individuals undergoing radiation, chemotherapy, or neurosurgery for brain tumors are also at higher risk.

Prognosis

Most cases of erythema multiforme (EM) are self-limited. In erythema multiforme minor, the lesions evolve over 1-2 weeks and ultimately subside within 2-3 weeks without scarring. However, the recurrence of erythema multiforme minor is common (up to one third of cases) and mostly preceded by apparent or subclinical herpes simplex virus (HSV) infection.

Erythema multiforme major has a mortality rate of less than 5% and is directly proportional to the total body surface area of sloughed epithelium. It usually has a more protracted course than erythema multiforme minor; clearing may require 3-6 weeks. Skin lesions usually heal with hyperpigmentation and/or hypopigmentation. Scarring is usually absent, except after secondary infection. Sepsis secondary to loss of the cutaneous barrier is the principle cause of death.

Advanced age, visceral involvement, increased serum urea nitrogen level, and previous bone marrow transplantation are poor prognostic factors. Surprisingly, although the incidence of erythema multiforme is increased among individuals with human immunodeficiency virus (HIV) infection (approaching 1 case per 1000 individuals per year), they do not appear to have a higher mortality rate.

Continuous and persistent erythema multiforme

Two additional rare clinical forms of erythema multiforme have been reported. Continuous erythema multiforme manifests as a prolonged course with overlapping attacks and may be associated with systemic administration of glucocorticoids.

Persistent erythema multiforme has a protracted clinical course over months, is commonly associated with atypical skin lesions, and is commonly resistant to conventional treatment. It has been reported in association with inflammatory bowel disease (IBD), occult renal carcinoma, persistent or reactivated Epstein-Barr virus (EBV) infection, and HSV infection.

Patient Education

Educate patients with erythema multiforme (EM) about appropriate symptomatic treatment, and provide reassurance that disease is usually self-limited. In addition, advise patients of the significant risk of recurrence and emphasize the avoidance of any identified etiologic agent. (See Monitoring and Prevention.)

For patient information, see [Skin Conditions & Beauty Center](#), as well as [Life-Threatening Skin Rashes](#) and [Image Collection: Picture of Erythema Multiforme Minor](#).

Clinical Presentation

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