Erythema multiforme

What is erythema multiforme?

Erythema multiforme is a hypersensitivity reaction usually triggered by infections, most commonly herpes simplex virus (HSV). It presents with a skin eruption characterised by a typical target lesion. There may be mucous membrane involvement. It is acute and self-limiting, usually resolving without complications.

Erythema multiforme is divided into major and minor forms and is now regarded as distinct from Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Who gets erythema multiforme?

Erythema multiforme most commonly affects young adults (20–40 years of age), however all age groups can be affected. There is a male predominance but no racial bias.

There is a genetic tendency to erythema multiforme. Certain tissue types are more often found in people with herpes-associated erythema multiforme (HLA-DQw3) and recurrent erythema multiforme (HLA-B15, -B35, -A33, -DR53, -DQB1*0301).

What triggers erythema multiforme?

Infections

Infections are probably associated with at least 90% of cases of erythema multiforme.

The single most common trigger for developing erythema multiforme is herpes simplex virus (HSV) infection, usually herpes labialis (cold sore on the lip) and less often genital herpes. HSV type 1 is more commonly associated than type 2. The herpes infection usually precedes the skin eruption by 3–14 days.

Mycoplasma pneumonia (a lung infection caused by the bacteria Mycoplasma pneumoniae) is the next most common trigger.

Many different virus infections have been reported to trigger erythema multiforme including:

- Parapoxvirus (orf and milkers' nodules)
- Herpes varicella zoster (chickenpox, shingles)
- Adenovirus
- Hepatitis viruses
- Human immunodeficiency virus (HIV)
- Cytomegalovirus
- Viral vaccines

Dermatophyte fungal infections (tinea) have also been reported in association with erythema multiforme.

Drugs

Medications are probably an uncommon cause (<10%) of erythema multiforme. If this diagnosis is being seriously considered then alternative drug eruptions should be excluded, such as SJS/TEN, generalised fixed drug eruption, polymorphic exanthematous drug eruption and urticaria.

Many drugs have been reported to trigger erythema multiforme, including barbiturates, non-steroidal anti-inflammatory drugs, penicillins, sulphonamides, phenothiazines and anticonvulsants.

Clinical features of erythema multiforme

General symptoms

There are usually no prodromal symptoms in erythema multiforme minor. However, erythema multiforme major may be preceded by mild symptoms such as fever or chills, weakness or painful joints.
Skin lesions

Typically in erythema multiforme, few to hundreds of skin lesions erupt within a 24-hour period. The lesions are first seen on the backs of hands and/or tops of feet, and then spread along the limbs towards the trunk. The upper limbs are more commonly affected than the lower. Palms and soles may be involved. The face, neck and trunk are common sites. Skin lesions are often grouped on elbows and knees. There may be an associated mild itch or burning sensation.

The initial lesions are sharply demarcated, round, red/pink and flat (macules), which become raised (papules/palpable) and gradually enlarge to form plaques (flat raised patches) up to several centimetres in diameter. The centre of the papule/plaque darkens in colour and develops surface (epidermal) changes such as blistering or crusting. Lesions usually evolve over 72 hours.

The typical target lesion (also called iris lesion) of erythema multiforme has a sharp margin, regular round shape and three concentric colour zones:

- Centre is dusky or dark red with a blister or crust
- Next ring is a paler pink and is raised due to oedema (fluid swelling)
- Outermost ring is bright red.

Atypical target lesions show just 2 zones and/or an indistinct border.

The eruption is polymorphous (many forms), hence the ‘multiforme’ in the name. Lesions may be at various stages of development with both typical and atypical targets present at the same time. A full skin examination may be required to find typical targets, as these may be few in number.

Lesions show the Köbner (isomorphic) phenomenon, meaning they can develop at sites of preceding (but not concurrent or subsequent) skin trauma.

There is no associated swelling of face, hands or feet, despite these being common sites of rash distribution. However the lips are often swollen, especially in erythema multiforme major.

Mucous membrane involvement

Mucosal lesions, if present, typically develop a few days after the skin rash begins.

In erythema multiforme minor, mucous membrane involvement is absent or mild. Mucosal changes, if present, consist initially of redness of the lips and inside cheek. Sometimes blisters develop and quickly break to form erosions and ulcers.

In erythema multiforme major, one or more mucous membranes are typically affected, most often the oral mucosa:

- Most commonly lips, inside the cheeks, tongue
- Less commonly floor of the mouth, palate, gums.

Other mucosal sites affected may include:

- Eye
- Anus and genitals
- Trachea/bronchi
- Gastrointestinal tract.

Mucosal lesions consist of swelling and redness with blister formation. The blisters break quickly to leave large, shallow, irregular shaped, painful ulcers that are covered by a whitish pseudomembrane. Typically the lips are swollen with haemorrhagic crusts. The patient may have difficulty speaking or swallowing due to pain.

With mycoplasma pneumonia, the mucous membranes may be the only affected sites (mucositis). This can be severe and require hospitalisation due to difficulty eating and drinking. Whether this is a limited form of erythema multiforme has not been determined.

Erythema multiforme: mucosal involvement
Recurrent erythema multiforme

Erythema multiforme can be recurrent, with multiple episodes per year for many years. This is believed to be nearly always due to HSV-1 infection.

How is the diagnosis of erythema multiforme made?

Erythema multiforme is a clinical diagnosis, although skin biopsy may be required to exclude other conditions. The histology of erythema multiforme is characteristic but not diagnostic. It varies with the age of the lesion, its appearance, and which part is biopsied.

Other tests may be done looking for infections commonly seen in association with erythema multiforme, such as mycoplasma. For more detail, see: Erythema multiforme: histology & mechanisms.

Treatment of erythema multiforme

For the majority of cases, no treatment is required, as the rash settles by itself over several weeks without complications.

Treatment directed to any possible cause may be required such as oral aciclovir (not topical) for HSV or antibiotics (eg erythromycin) for Mycoplasma pneumoniae. If a drug cause is suspected then the possible offending drug should be ceased.

Supportive/symptomatic treatment may be necessary.

- Itch – oral antihistamines and/or topical corticosteroids may help.
- Oral pain – mouthwashes containing local anaesthetic and antiseptic reduce pain and secondary infection.
- Eye involvement should be assessed and treated by an ophthalmologist.
- Erythema multiforme major may require hospital admission for supportive care, particularly if severe oral involvement restricts drinking.

The role of oral corticosteroids remains controversial, as no controlled studies have shown any benefit. However for severe disease 0.5–1 mg/kg/d prednis(o)lone is often used early in the disease process.

Recurrent erythema multiforme is usually treated initially with continuous oral aciclovir for 6 months at a dose of 10 mg/kg/d in divided doses (eg 400 mg twice daily), even if HSV has not been an obvious trigger for the patient’s erythema multiforme. This has been shown to be effective in placebo-controlled double blind studies. However, erythema multiforme may recur when the aciclovir is ceased. Other antiviral drugs such as valaciclovir (500–1000 mg/d) and famciclovir (250 mg twice daily) should be tried if aciclovir has not helped; these drugs are not readily available in New Zealand.

Other treatments (used continuously) that have been reported to help suppress recurrent erythema multiforme include:

- Dapsone 100–150 mg/d
- Antimalarial drugs, eg hydroxychloroquine
- Azathioprine 100–150 mg/d
- Others: thalidomide, ciclosporin, mycophenolate mofetil, photochemotherapy (PUVA)

What is the outlook for erythema multiforme?

Erythema multiforme minor usually resolves spontaneously without scarring over 2 to 3 weeks. Erythema multiforme major can take up to 6 weeks to resolve. Erythema multiforme does not progress to SJS/TEN.

There may be residual mottled skin discolouration. Significant eye involvement in erythema multiforme major may result in serious eye problems, including blindness, as may occur with SJS/TEN.

Related information

References:

Erythema multiforme. DermNet NZ

On DermNet NZ:

- Erythema multiforme: histology and mechanisms
- Dermatological emergencies online course
- Bullous drug eruptions
- Drug eruptions
- Mycoplasma pneumoniae infection

Other websites:

- Erythema multiforme – Medscape Reference
- Erythema multiforme – British Association of Dermatologists

Books about skin diseases:

See the DermNet NZ bookstore

Author: Dr Amanda Oakley, Dermatologist, Hamilton, 1997. Updated by Dr Delwyn Dyall-Smith, 2009. Updated by Dr Oakley, October 2015.

DermNet NZ does not provide an online consultation service.
If you have any concerns with your skin or its treatment, see a dermatologist for advice.