CASE REPORT

Drug-mediated rash: erythema multiforme versus Stevens-Johnson syndrome

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SUMMARY

A 92-year-old woman presented with an acute onset generalised maculopapular rash with associated mucosal involvement, on a background of recent start of griseofulvin. The rash progressed rapidly over 2 days to involve most of her body, however, mucosal involvement was limited to her oral mucosa. Characteristic target lesions appeared at 72 h, and a diagnosis of erythema multiforme secondary to griseofulvin was made after further investigation and skin biopsy. The patient was monitored closely for progression of the rash and other indicators of more severe dermatological conditions such as Stevens-Johnson syndrome. She was managed symptomatically, with resolution of the rash in 4 weeks and full recovery to her premorbid level of functioning. This case details the diagnostic and management approach to erythema multiforme, a condition that warrants thorough consideration for the differential of Stevens-Johnson syndrome.

BACKGROUND

Erythema multiforme represents a spectrum of disease from localised rash and minimal mucosal involvement (erythema multiforme minor) to a more severe generalised rash with limited desquamation and involvement of mucous membranes with blister formation (erythema multiforme major). More severe cases of erythema multiforme may be confused with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), severe desquamating conditions that differ vastly in management and prognosis. It is therefore important to recognise the characteristic rash and lesions of erythema multiforme, its common triggers and the distinguishing clinical features between this self-resolving condition and more severe dermatological conditions to avoid patient misdiagnosis and mismanagement.

CASE PRESENTATION

A 92-year-old woman from low-level care presented with a 2-day history of diffuse maculopapular rash with mucosal involvement and malaise, in the setting of recent commencement of griseofulvin for onychomycosis.

She presented with a pruritic, maculopapular rash that began in the left axilla and back and progressed over 12 h to involve the face, upper limbs and trunk. The patient also developed marked lip swelling and oral ulcers with no associated stridor or dyspnoea. She presented to her local general practitioner, where she was given 100 mg hydrocortisone intramuscular and sent to the emergency

department of a local hospital where she was admitted under the general medicine team.

Following the hydrocortisone injection, the patient reported marked reduction of her lip swelling, but no improvement to the rash, which progressed over the next 12 h to involve the lower legs. Her oral ulcers were painful and severely limited her ability to tolerate oral intake. She was found to be febrile at 38.3°C, but denied any infective symptoms such as cough, shortness of breath, abdominal pain, dysuria or rigours.

The patient reported no previous episodes of a similar nature. She was otherwise well prior to admission, and denied sick contacts or recent travel. She had started griseofulvin for nail changes 2 weeks prior to the development of the rash, but denied any acute reactions to the medication. There have been no other medication changes. Her medical history is notable for an undifferentiated symmetrical polyarthropathy of the hands, hypertension and aortic stenosis. There is no medical or family history of dermatological disorders, or prior infection with herpes simplex or *Mycoplasma pneumoniae*. The patient is allergic to codeine but nil else, and does not smoke cigarettes or drink alcohol.

On examination by the medical team, the patient appeared not unwell looking, and was orientated to time and place. She was haemodynamically stable and afebrile, and there were no signs of meningism. A diffuse erythematous, maculopapular, blanching rash was noted, affecting the torso, bilateral upper and lower limbs, face, neck and scalp (figures 1 and 2). An erythematous plaque was noted in the left axilla. Several well-demarcated target lesions of three concentric zones were noted on the back (figure 3). These consisted of a central darker red area, surrounded by a paler pink zone and a peripheral red ring. There was no ulceration, blistering or excoriation and no evidence of trauma or superimposed cellulitis.

Examination of the oral cavity revealed several ulcers affecting the lower lip and soft palate, with some mild lip swelling. There was no extension into the pharynx.

Ophthalmological examination revealed no iritis or uveitis and no conjunctival involvement. Genital and anal examination revealed no ulceration.

INVESTIGATIONS

Routine biochemistry was performed which revealed normal red and total white cell counts, normal electrolytes and renal and liver function. On admission, her eosinophil count was normal at

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Figure 1 Extensive erythema multiforme rash over the patient's back, with clear target lesions.

0.10, but mildly rose over the next 3 days to peak at 0.65, before settling.

A septic screen was performed which was negative apart from mild elevation of C reactive protein and erythrocyte sedimentation rate at 78 and 40, respectively. Her chest X-ray showed changes of unknown significance, unconvincing for

consolidation. PCR for herpes simplex virus (HSV) and *Mycoplasma* serology were negative. Viral hepatitis and HIV serologies were also negative.

A thorough autoimmune screen including antinuclear antibody and extractable nuclear antigens returned negative.

Three cutaneous punch biopsies were performed on the lateral abdomen and right medial-distal thigh. They revealed interface dermatitis with basal vacuolation and a degree of exocytosis and spongiosis. Moderate superficial perivascular infiltration of lymph-histiocytic cells, including a few pyknotic cells, intracapillary polymorphs and scattered eosinophils was seen. Occasional dyskeratotic cells were noted but there were no necrotic keratinocytes. There was no vasculitis, acantholysis, HSV-inclusions or multinucleated giant cells. Immunofluorescence for IgA, IgG, IgM and C3 was negative. Appearances in these biopsies are consistent with erythema multiforme, with no findings suggestive of SJS/TEN.

Given the patient's age and rapid clinical response, no further investigations, such as patch testing or a drug-induced lymphocyte stimulation test, were performed as inpatient or outpatient to confirm the causative drug.

DIFFERENTIAL DIAGNOSIS

At initial presentation to the hospital 48 h after onset of the rash, dermatology consult suggested a diagnosis of pemphigus vulgaris, an autoimmune disease characterised by mucocutaneous blisters and erosions. Although the patient did not exhibit any clear cutaneous blisters, she had significant oral mucosal blistering and ulceration.

An important differential at this point was that of SJS, an acute and serious immune-complex-mediated hypersensitivity reaction involving the skin and mucous membranes, typically secondary to medication use. Though she was febrile at

Figure 2 Involvement of lower limbs.

Figure 3 A close up of typical target lesions.

presentation, this was thought to be less likely given the limited involvement to one mucosal surface, non-tender rash and the absence of cutaneous blistering, ulceration or detachment.

Examination of the patient at 72 h revealed new target lesions on her back, raising the differential of erythema multiforme, a hypersensitivity reaction often triggered by infections such as HSV, *M. pneumoniae* or less commonly, medication use. This diagnosis was also supported by the skin biopsy findings. Herpes simplex infection was ruled out through PCR of swabs from oral ulcers and skin. *Mycoplasma* and other viral serologies were also negative. The patient was therefore diagnosed with erythema multiforme major secondary to griseofulvin.

TREATMENT

Erythema multiforme is typically a self-resolving condition that is managed symptomatically with treatment of possible underlying causes. In this patient, griseofulvin was ceased on admission as a potential trigger for her rash. She was started on intravenous acyclovir 250 mg thrice daily for empiric treatment of herpes simplex, which was ceased following the negative PCR.

The patient was initially febrile with a non-conclusive chest X-ray. Antibiotics were withheld due to her haemodynamic stability and the desire to avoid antibiotic therapy, which is known to worsen SJS, a differential at the time. The patient responded well to paracetamol in the emergency department and remained afebrile for the duration of her admission.

The patient's vital signs and electrolytes, liver function and full blood counts were monitored daily. The patient was monitored closely for progression of her rash and oral ulceration. Extension of mucosal involvement to the tracheobronchial tree was of particular concern given the risk of acute respiratory distress syndrome.

Symptomatically, the patient was placed on oral loratadine 10 mg twice daily, and topical β -methasone dipropionate 0.05% ointment, for her pruritus. She was given chlorhexidine 0.2% mouthwash three times a day and lignocaine 2% gel 10 mL, four hourly to manage her pain and prevent secondary infection of her oral lesions. Her oral intake and fluid balance were monitored closely to ensure adequate nutrition and fluid status.

OUTCOME AND FOLLOW-UP

The patient's rash and oral ulcers resolved gradually over a 4-week period, with no scarring or skin discolouration. She was able to return to her low-level care facility and resume her pre-morbid level of functioning.

DISCUSSION

Erythema multiforme is an acute immune-mediated disorder that presents with a distinctive clinical and histological response to a number of different stimuli. It typically occurs between 20 and 40 years of age, though it can affect all ages.¹ It is most commonly triggered by infection with HSV or *M. pneumoniae* infection, or less commonly, as a result of medications such as sulphonamides, non-steroidal anti-inflammatories and penicillins.²

There have been a small number of documented cases in the literature associating griseofulvin and erythema multiforme, though this is extremely uncommon.^{3 4} Griseofulvin acts by interfering with the fungal mitotic spindle, thereby inhibiting cell wall synthesis. It is an effective and well-tolerated antifungal agent.⁵

Erythema multiforme may present with varying severity, and has been classified into two forms: the less severe erythema multiforme minor, and the more severe erythema multiforme major. While both forms involve the development of a diffuse maculopapular rash and typical 'target' or 'iris' cutaneous lesions, the extent of mucosal involvement varies, with erythema multiforme minor having minimal if any mucosal involvement.⁶ Erythema multiforme major may have mild prodromal symptoms such as arthralgia and weakness.⁷

There has been previous controversy regarding the definition of erythema multiforme and SJS as either a spectrum of a single disease process or separate conditions. A consensus definition has since separated the two entities according to clinical presentation.⁶ Erythema multiforme major classically presents with typical target or atypical raised target lesions predominantly on the limbs but also the trunk and face, whereas SJS usually presents with atypical flat target lesions or widespread purpuric macules truncally. Desquamation is a clear clinical differentiator between erythema multiforme major and SJS, with desquamation in erythema multiforme major limited to 1–2% of the body surface area, compared to SJS, which is higher but less than 10% and TEN being greater than 30% of the body surface area.⁸

Erythema multiforme is a clinical diagnosis, though a skin biopsy may have diagnostic value in excluding other differentials. While the histology may depict typical changes of vacuolar interface dermatitis with spongiosis and partial thickness epidermal necrosis, the results vary dependent on the timing and location of the biopsy and should be used only as a guide to diagnosis.⁹ Classically, there is prominent accumulation of mononuclear cells in the epidermis in erythema multiforme, with more dermal inflammation and individual keratinocyte necrosis compared with SJS/TEN. In contrast, SJS/TEN is characterised by a paucity of inflammatory infiltrate in the dermis and epidermis, with large sheets of epidermal necrosis. On immunochemistry, the earliest EM lesions display a greater accumulation of T-lymphocytes in the epidermis and superficial dermis, while early SJS/TEN lesions typically display dense

Learning points

- ▶ Erythema multiforme is an uncommon mucocutaneous condition that is most commonly triggered by herpes simplex virus and *Mycoplasma pneumoniae*.
- ▶ While less common, medications have been reported to trigger erythema multiforme. Alternative causes of drug-induced rash, such as fixed drug eruptions, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and urticaria must be considered.
- ▶ Classic target or iris lesions are characteristic of erythema multiforme though atypical target lesions may appear in other conditions including SJS.
- ▶ Target lesions may not appear until several days after onset of the rash.
- ▶ It is important to differentiate between erythema multiforme major and SJS/TEN as they markedly differ in management and prognosis. Individuals with suspected erythema multiforme should be monitored early in the course of the illness for signs of desquamation that may raise clinical suspicion of SJS/TEN.

macrophage infiltration in the dermis and epidermis, and significant TNF- α immunoreactivity in the epidermis.¹⁰

Erythema multiforme is a self-resolving condition, with management centred on treating or reversing possible causes. Antihistamines, topical corticosteroids and topical analgesia may be used to provide symptomatic relief.¹¹ However, patients with suspected erythema multiforme major should be monitored early on for signs of desquamation or changes in rash that might suggest SJS or TEN, which are similarly mucocutaneous hypersensitivity reactions but may require closer monitoring and more intensive management in a specialised burn unit.¹²

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