

## Drug induced erythema multiforme: A case report

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### Abstract

Erythema multiforme is an uncommon, immune-mediated, acute mucocutaneous condition affecting the skin and mucous membranes. It has various etiological factors, including Herpes Simplex virus, medications, auto-immune diseases and malignancies, but the most common cause is infection by Herpes Simplex virus. The characteristic feature is the presence of "target lesions". Diagnosis is made by clinical signs and symptoms, along with laboratory tests and histopathological examination when required. It should be differentiated from Urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruptions and other vesiculobullous diseases like Pemphigus. Treatment includes symptomatic or supportive care along with corticosteroids, antivirals if needed and hospitalization in extreme cases. In the present case of drug induced Erythema multiforme, the offending drug was immediately stopped and patient was treated with topical and systemic corticosteroids along with symptomatic treatment, leading to immediate and complete resolution of the symptoms.

**Keywords:** Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, Erythema multiforme major, Erythema multiforme minor, Vesiculobullous diseases, Herpes Simplex virus.

### Introduction

Erythema multiforme (EM) is an acute, immune-mediated, mucocutaneous condition, with the most common etiology being Herpes Simplex virus (HSV) infection and the use of certain drugs or medications.<sup>1,2</sup> Erythema multiforme minor (EMm), Erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN or Lyell disease) are the four major variants in which EM was classified previously.<sup>3-5</sup> These four variants are still considered as a single disease entity by many authors, although they may differ in clinical severity. Others consider EM different from SJS and TEN, since EM has a strong association with HSV infection, wherein SJS and TEN seem to be more commonly induced by various medications. EM, SJS, and TEN may have overlapping clinical signs and symptoms but may differ in cutaneous findings.<sup>1,4-9</sup>

There are numerous etiological factors in the medical literature linked to the development of EM, which include infections, certain medications (like NSAIDs, anticonvulsants, penicillins, sulphonamides), malignancy, autoimmune diseases, radiation, immunization, and menstruation etc, of which infection by HSV is the most common.<sup>2,4,10</sup> Mycoplasma pneumoniae is another bacterial infectious agent, which has a well documented association with the development of EM, especially in children.<sup>10,11</sup> Drug induced EM is rare in occurrence and has been reported in less than 10% of the cases, the most common culprits being nonsteroidal anti-inflammatory drugs, sulfonamides, antiepileptics, and antibiotics.<sup>2,10</sup>

Hereby presenting a rare case of Erythema Multiforme in an 80 year old adult male, predominantly affecting the oral cavity, caused by medication use.

### Case Report

An 80 year old male, reported with a chief complaint of pain and ulcers in mouth along with blackish discoloration on hands, feet and buttocks since last 4-5 days, after taking medication (amoxicillin) for abscess in his left toe. Ulcers in mouth were painful (severe, pricking type, continuous and localised pain) and the patient was unable to eat, drink or carry out his daily activities. Patient was afebrile with all vital signs within normal limits and his medical history was non-contributory. Extra-oral examination revealed multiple dark brown-black well defined round areas of discoloration, accompanied with itching, seen on palms and back of hands (Fig. 1), feet (Fig. 2), as well as on buttocks. Lips showed multiple, diffused, irregular erythematous areas measuring 0.5 x 0.5 cm on vermilion borders. Intra-orally diffuse, multiple, irregular mixed, red and white lesions were seen on left (Fig. 3) and right buccal mucosa (Fig. 4), measuring 1 x 1 cms to 1 x 2 cms, surrounded by erythematous margins and covered with white slough. Lesions were tender on palpation, soft in consistency, with no pus/blood discharge and Nikolsky's sign being negative. Based on the history and clinical examination, a provisional diagnosis of EM was given and Urticaria, Steven-Johnson Syndrome, Fixed drug eruption and Mucositis were considered in Differential Diagnosis. After conducting various blood tests (CBC, TLC, DLC, RBS, RFT, LFT, ESR) patient was told to stop all medications and was prescribed a topical steroid ointment (clobetasol) TID, a topical anti-fungal ointment (candid) TID, systemic steroid (Prednisolone 20 mg BD) for 7 days along with a multivitamin and an antacid. Patient when recalled after 1 week, showed

marked improvement in his condition and is now on periodic recall with no signs of recurrence.



**Fig. 1:** Well defined, multiple dark brown-black round areas of discoloration, with itching, seen on back of hands



**Fig. 2:** Well defined, multiple dark brown-black round areas of discoloration, with itching, seen on feet also



**Fig. 3:** Intra-oral lesions of EM showing diffuse, multiple, mixed, red and white patches covered with white slough on left buccal mucosa



**Fig. 4:** Intra-oral lesions of EM showing diffuse, multiple, mixed, red and white patches covered with white slough on right buccal mucosa

### Discussion

The present case lays emphasis on drug induced EM and its oral manifestations. Although many cases of EM are reported in the literature, EM manifesting predominantly in the oral cavity is rarely reported. EM occurs predominantly in young adults, and is commonly seen between the second and fifth decades of life.<sup>1,5,10</sup> Mucosal lesions in EM generally occur with a frequency of approximately 25–60%.<sup>10</sup> Mucosal involvement usually occurs simultaneously with skin involvement, although it can precede or follow the

onset of skin lesions by several days and in rare cases, patients may exhibit mucosal lesions in the absence of cutaneous involvement.<sup>12</sup> In our case, the patient presented with oral manifestations prior to skin manifestations.

Almost, 70% of patients with EM show oral manifestations which include swollen, cracked and crusted lips, bleeding, and intraoral lesions on the non-keratinised mucosa, more common in the anterior parts of the mouth. The presence of diffuse, widespread macules which further form blisters and ulcers, make it clinically difficult to differentiate it from other vesiculobullous disorders.<sup>3</sup>

Skin lesions in EM minor are usually in the form of macules or erythematous papules that develop into classic target or iris lesions in a symmetrical distribution, and occasionally leading to bullae formation. "Typical targets" are defined as individual lesions which are less than 3 cm in diameter, have a regular round shape, a well-defined border, and two concentric palpable oedematous rings, paler than the centre disc, whereas "Raised atypical targets" are more commonly seen in severe EM major and Stevens–Johnson syndrome, and are similar in appearance, but palpable.<sup>3</sup>

EM minor, generally shows involvement of a single mucous membrane, most commonly being the oral mucosa.<sup>13</sup> It is often also characterised by symmetrically distributed rashes, on the extensor surfaces of the arms and legs, which are typically "iris" or "target" lesions or bullae on extremities, and may itch.<sup>14</sup>

The severity of the lesions is more in EM major with involvement of multiple mucous membranes such as the oral cavity, genital, ocular, laryngeal, or oesophageal mucosae, or a combination. The skin lesions are generally similar to those of EM minor but may be atypical, raised and can include bullae.<sup>13</sup>

Stevens–Johnson syndrome and EM constitute two distinct entities showing similar mucosal erosions but different patterns of cutaneous disease.<sup>15</sup> Unlike EM, SJS is characterised by widespread erythematous or purpuric macules or atypical target lesions, which are macular rather than papular.<sup>8,15</sup> Also, lesions in SJS are typically more prominent on the trunk and spread distally, whereas in EM, lesions classically show an acral predominance. The most common cause of SJS are the drugs or medications, hence there is an urgent need to stop or discontinue the offending drug.<sup>16</sup> Since it is histopathologically difficult, to distinguish between severe EM and SJS, so clinical signs and symptoms should be used to reach a reliable diagnosis. SJS normally manifests as a more extensive epidermal necrosis with fewer inflammatory cells as compared to EM.<sup>17</sup> Also, due to the fact that constitutional symptoms often accompany SJS, hence immediate diagnosis is mandatory, since the possibility of life threatening

complications and risk for progression to toxic epidermal necrolysis is high.<sup>8,16</sup>

Stevens–Johnson syndrome (SJS) is more severe than EM major, causing widespread lesions affecting the skin; oral cavity, eyes, pharynx, larynx, oesophagus, genitals, and sometimes also manifests as flu-like symptoms, fever, sore throat, headache, arthralgias, myalgias, pneumonia, nephritis, or myocarditis. Ocular changes resembling those of mucous membrane pemphigoid – dry eyes and symblepharon – may also occur in SJS, and it may be followed by sicca syndrome, or even Sjögren's syndrome.<sup>18</sup>

SJS was considered in the differential diagnosis of the present case as the triggering factor was medication, but was ruled out due to the acral presentation of the lesions. The clinical appearance of diffuse and widespread oral ulceration can make it difficult to differentiate EM from other vesiculobullous disorders such as pemphigus or pemphigoid. EM should also be differentiated from viral stomatitis, and toxic epidermal necrolysis.<sup>14</sup> Features which favour EM are the acute onset (or recurrent nature), oral erosions typically located on the lip and anteriorly in the mouth, and pleomorphic skin and other lesions. In the present case Pemphigus was ruled out due to acute nature of the lesion, rapid healing and typical skin lesions.

No specific objective markers or criteria are required for the diagnosis of EM. The important clues to diagnosis continue to be the clinical history along with clinical findings. Pertinent components of the history include: (i) an acute, self-limiting or episodic course; (ii) signs and symptoms of associated infections, such as HSV or M. pneumonia infection and (iii) a history of the use of recent or new medications. Clinical clues to diagnosis, include the presence of target lesions, raised atypical papules or mucosal involvement, or a combination of these.

Laboratory studies and skin biopsies are not required in all cases of EM, although they may assist in confirming the diagnosis, determining the inciting factor and ruling out other diseases in the differential diagnosis.<sup>19</sup> Histopathologic changes are not always diagnostic of EM, but can be helpful in excluding other disorders.<sup>19</sup> In the above case, histopathology was not performed as the patient was non-compliant. A complete blood count (CBC), measurement of urea and electrolytes, erythrocyte sedimentation rate (ESR), and liver function tests (LFTs) together with HSV and mycoplasma serology; and microbial cultures from blood, sputum, and erosive areas should be taken in severe cases.<sup>3</sup> All the blood investigations in the present case were within normal limits.

There are no specific diagnostic tests for EM, hence the diagnosis is usually supported by perilesional tissue biopsy and exclusion of other causes. Histological examination and immunostaining often show intraepithelial oedema and spongiosis early on, with satellite cell necrosis (individual eosinophilic

necrotic keratinocytes surrounded by lymphocytes), vacuolar degeneration of the basement membrane zone, and severe papillary oedema with sub-epithelial or intra-epithelial vesiculation. There is intense lymphocytic infiltration at the basement membrane zone and perivascularly, and non-specific immune deposits of IgM, C3, and fibrin at these sites. However, signs can be variable and immunostaining is not specific for EM.

Any precipitants should be removed or treated. Causal drugs should be stopped and relevant infections treated. Antiviral agents may be indicated in Herpes Virus associated EM, and a 5-day course of acyclovir 200 mg five times daily at the first sign of lesions, or 400 mg four times daily for 6 months, or continuous treatment using valacyclovir, 500 mg twice a day, is useful as prophylaxis. Tetracycline 250 mg four times a day for at least one week may be indicated in EM related to *Mycoplasma pneumoniae*.<sup>3</sup>

No specific treatment is available for EM itself, but symptomatic treatment like analgesics and a liquid diet may be needed. In severe forms of EM, hospital and supportive care are often required: intravenous fluids, early ophthalmological and dermatological consultations may also be done.<sup>3</sup>

Corticosteroids are the most commonly used drugs in the management of EM, despite the lack of evidence. EM minor may respond to topical corticosteroids. Patients with EM major or Stevens–Johnson syndrome should be treated with systemic corticosteroids (prednisolone 0.5–1.0 mg/kg/day tapered over 7–10 days) or azathioprine, or both, or other immunomodulatory drugs<sup>20</sup> such as cyclophosphamide, dapsone, cyclosporin, levamisole, thalidomide,<sup>21,22</sup> or interferon  $\alpha$ .<sup>23,24</sup> Cyclosporin given intermittently may control recurrent EM.<sup>24</sup>

## Conclusion

EM, SJS, and TEN have many overlapping clinical signs and symptoms, which further are sometimes difficult to distinguish from other vesiculobullous lesions affecting the oral mucosa, hence a thorough knowledge along with excellent clinical skills are required to make a correct diagnosis of the condition. Lab investigations and histopathological examination may also aid in the diagnosis. In the above case, prompt diagnosis and immediate treatment given to the patient not only cured the patient, but also prevented the lesions from becoming more severe, thereby saving the patient from major discomfort and pain. The prognosis in some cases is very good, provided the lesions are diagnosed and treated at the earliest, thereby again emphasizing on the fact that the clinician should be well versed with the theoretical as well as the clinical skills in diagnosing the diseases of the oral cavity.

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