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CASE REPORT

Drug-induced Erythema Multiforme Major in an Elderly Female

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Abstract

Erythema multiforme (EM) is an acute, immune-mediated condition which affects the skin and mucous membranes. EM is a type 4 hypersensitivity reaction typically mediated by cytotoxic T lymphocytes. It is usually a self limiting, transient, inflammatory disease that spontaneously resolves within weeks without major sequelae. However, occasionally patients might have frequent recurrences, persistent disease or serious complications like fluid and electrolyte abnormalities. The most common triggers are infection followed by medications. Here we present the case of an 81-year-old female who came in with worsening lip and tongue swelling associated with a rash and was diagnosed with EM major due to naproxen.

Keywords: Erythema multiforme major, Erythema multiforme minor, Non-steroidal antiinflammatory drug, Herpes simplex virus, Naproxen

1. Introduction

The term erythema multiforme (EM) was first coined by Ferdinand von Hebra in 1860.[1] Erythema multiforme is a self limiting, acute, immune mediated, inflammatory mucocutaneous disorder characterized by distinctive target-like skin eruptions with or without oral mucous membrane lesions.[1,2] The main differentiating features between erythema multiforme major (EMM) and erythema multiforme minor(EMm) is mucous membrane involvement and associated systemic symptoms like fever and arthralgias which is seen in EMM.[1,2] A variety of factors have been implicated in the pathogenesis of EM. Most common inciting factors are infection, mainly herpes simplex virus, and medications.[1,2] Here we are presenting a case of EMM due to naproxen.

2. Case presentation

An 81-year-old female with a history of hypertension on lisinopril for many years presented with progressive lip swelling and a rash for 3 days. The rash had started suddenly; initially it was made up of small, rounded, vesicular lesions on her extremities, most notably on her palms and soles, which evolved into targetoid lesions. She also complained of lip swelling and skin peeling. She denied fever, flu-like symptoms, urinary symptoms, joint pain, myalgias, changes in her bowel habit, as well as recent changes in diet, body products or her living environment. She denied a history of similar episodes in the past. She was allergic to sulfonamides, lisinopril and iodinated contrast media.Upon further questioning, she had been having back pain for a week, for which he had been taking naproxen. At the time of presentation she was afebrile, had a heart rate 80 beats/min, and a blood pressure of 143/80 mm Hg. On physical examination she had a bilateral and symmetrical rash made up of well-defined, rounded, target-like lesions on affecting the distal segments of her extremities, mainly the palms and soles; some of these lesions had developed superficial ulceration and crusting in the center surrounded by three zones of erythematous halos. She also had superficial ulcerations and desquamation of her lips. No bullae were noted (Figs. 1–3). She

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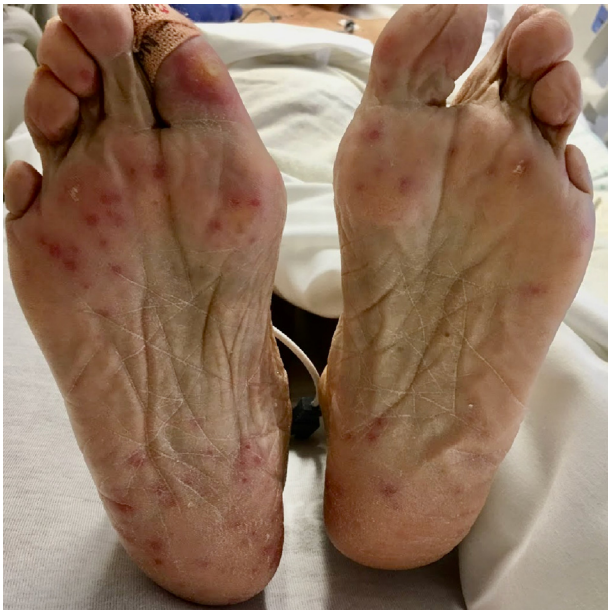

Fig. 1. Target like lesions in the soles.

was started on oral prednisone 40 mg once daily and antihistamines as needed for itching. Barrier lip and skin ointment were used for symptomatic management of her lesions. A skin biopsy from one of the lesions in the extremities showed necrotic keratinocytes (Fig. 4). ANA was negative which ruled out systemic lupus erythematosus (SLE), SLE can be associated with EM-like lesions. Non-steroidal antiinflammatory drugs (NSAID) were added to the allergy list and she was advised to avoid NSAID for life. Her lesions improved rapidly with treatment and she was discharged after 4 days on a tapering course of oral prednisone for two additional weeks.

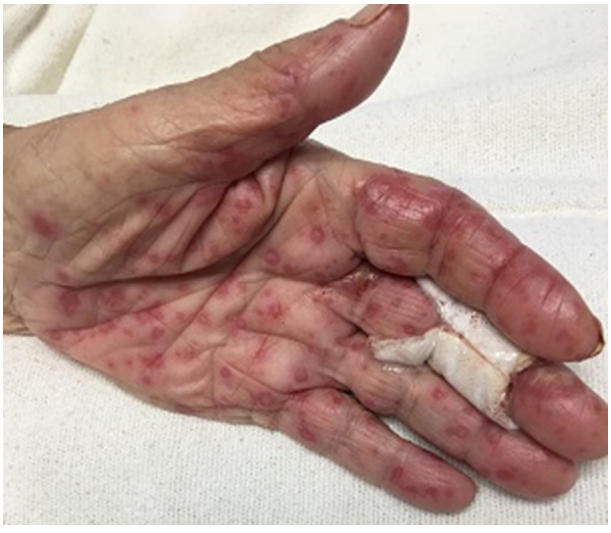

Fig. 2. Target like lesions in the palms, some of them with double halos.

At a 6-month follow up she had complete resolution of the lesions without recurrence.

3. Discussion

EM is an acute, typically self limited mucocutaneous inflammatory and hypersensitivity reaction characterized by a distinctive target like skin eruption with or without oral or other mucous membrane involvement.[1] It has been classified as EMM or EMm based on the degree of mucosal involvement and extent of lesions.[1] In EMM there is severe mucosal involvement and may have associated systemic symptoms such as fever and arthralgias; however EMm refers to EM without or with only mild mucosal disease and associated systemic symptoms.[1,2] In the past EM was on the different spectrum of disease such as a Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); however, now it is recognised as a distinct clinical entity.[1]

The annual incidence is unknown due to the fact that minor forms are not reported and does not required hospitalization, it is estimated to be far less than 1 percent.[1–3] It has a predilection for young adults between the ages of 20 and 40 years.[3,4] EMM is more frequently seen in females while EMm has slight male predominance.[1,3] No racial predominance has been noted based on our literature review.[1–3] EM can also occur in children and older adults.[3]

EM is caused by a cell-mediated immune mechanism,[1,3] This type of immune mediated reaction is seen with a variety of antigens; among these infectious agents account for 90% of cases, Herpes simplex virus (HSV) 1 is the most common followed by *Mycoplasma pneumoniae* especially in children.[1,2] HSV 2 is also sometimes associated with EM.[1,2]

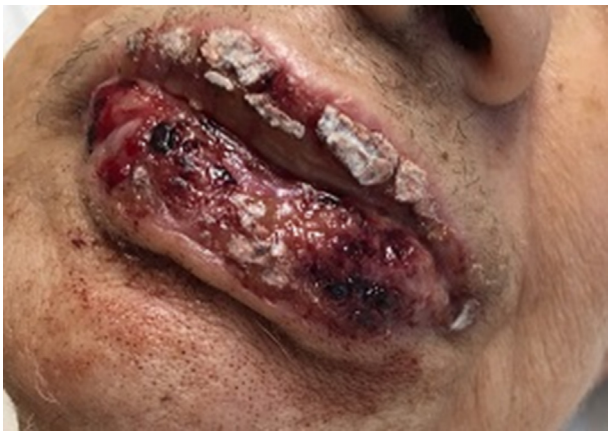

Fig. 3. Demonstrating a lip ulceration.

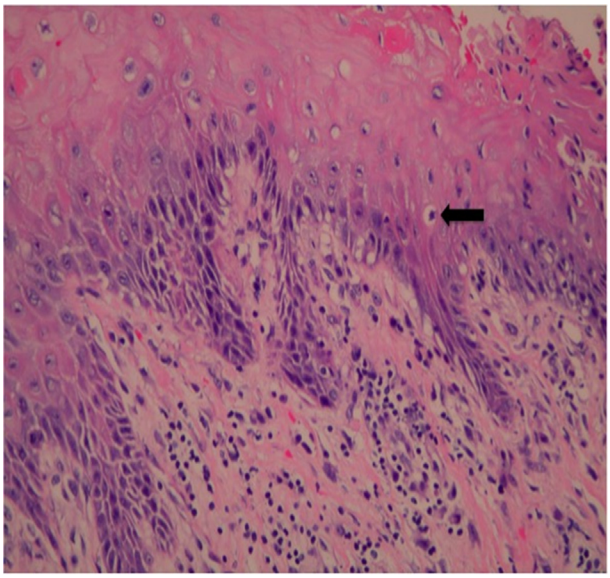

Fig. 4. H&E stain, high power field, demonstrating necrotic keratinocytes (black arrow).

Many conditions have been implicated in the pathogenesis of including a variety of viral and bacterial infections, drugs, malignancies, autoimmune diseases, radiation, immunizations, pregnancy, menstruation, chemicals and food products.[2] Less than 10% of cases are associated with medications[3]; however, based on some of the literature it can be up to 50%.[3] Medications that have been commonly identified as causes of EM include NSAID, sulfa drugs, anticonvulsants, tyrosine kinase inhibitors, biologic agents such as a tumor necrosis factor alpha inhibitors, phosphoinositide 3-kinase inhibitors and retinoids.[2,3] EM has also been associated with autoimmune diseases like inflammatory bowel disease, hematological malignancies like leukemia and lymphoma and some solid malignancies like renal cell carcinoma and gastric adenocarcinoma.[2] Vaccines such as measles, mumps and rubella, hepatitis B and pneumococcal vaccines have also been linked to EM.[2]

Increased disease susceptibility with HLA associated alleles has also been reported, especially HLA DQ3 is associated with recurrent EM.[5] The main chemokine found in drug-associated EM is tumor necrosis factor alpha while interferon gamma is more commonly found in HSV associated EM.[2,5] HSV genes are expressed on antigen expressing keratinocytes which in turns recruit T helper cells and release interferon gamma which in turn leads to subepithelial and intraepithelial vesiculation complicated by extensive blistering and erosions.[1,5]

Lesions develop 10–14 days after the initial HSV infection and usually resolve within 2 weeks.[3] Some lesions can persist for up to 5 weeks.[2] The term multiforme describes a myriad of clinical manifestations. EM most often manifests with combined cutaneous and mucosal features; sometimes only cutaneous or mucosal lesions can be seen.[5] Typical three component target or iris lesions are the hallmark of EM however it these are not always present.[2,5] Oral involvement is seen in 70% cases.[1,3,4] The most commonly affected sites are the vermilion border of lip and the buccal, labial and lingual mucosal surfaces.[1,3] The appearance of the rash can make it difficult to distinguish from other vesiculobullous lesions.[4] The skin lesions in EMm are usually symmetrical typical targetoid lesions in extremities.[4] The lesions in EMM are more atypical and often palpable.[4] Sometimes it can involve the eyes and lacrimation and photophobia can be the initial presentation.[1] Prodromal symptoms are uncommon in mild cases and but can be seen when there is significant mucosal involvement.[2,5]

The history and physical examination are essential for diagnosis of EM, if needed skin biopsy helps to confirm diagnosis.[1,2] Histopathology sometimes helps to rule out other diseases like lupus erythematosus or vasculitis.[2] Biopsy results depend on the site of biopsy and the timing of the lesion.[2] Characteristic pathological findings include necrotic keratinocytes, spongiosis, focal vacuolar degeneration of basal keratinocytes and as the inflammatory reaction evolves, perivascular inflammatory infiltrate and exocytosis.[4,5] No specific laboratory abnormalities have been identified except in very severe cases of EM where there can be elevated levels of erythrocyte sedimentation rate, white blood cells and liver enzymes.[1,5]

Our differential diagnosis included a wide range drug induced mucocutaneous eruptions like SJS, urticaria, fixed drug eruption, SLE, bullous pemphigoid and hypersensitivity reactions.[2] SJS usually presents with widespread atypical targetoid lesions and macules; more severe with worse systemic involvement and manifestations as compared to EM.[5] Urticaria lesions usually disappears within 24 h as compared to fixed lesions of EM.[2,5] Itching is more pronounced in urticaria.[5] Fixed drug eruption is a hypersensitivity reactions to specific drugs with fewer lesions usually occurs within 8 h of re-exposure to the culprit drug.[2] The mainstay of treatment is to stop the suspected triggering agent.[1,5] No specific treatment has been identified.[1,6] Most mild cases can be managed symptomatically as an outpatient or might required topical corticosteroids.[1,6,7] Severe forms causing fluid and electrolyte imbalances require hospitalization, intravenous fluids and standard systemic corticosteroids, for

example prednisone at a dose of 0.5–1 mg/kg/day.[1,6] Immunosuppressants like cyclosporine, azathioprine, cyclophosphamide and thalidomide are sometimes used alone or in combination with steroids.[1,3–5] Antiviral therapy is reserved for recurrent EM.[2,3]

Based on our literature review only one case of naproxen induced erythema multiforme has been reported in a 4 year old girl who had a history of carbamazepine induced SLE and developed EM. There are few case reports linking different NSAIDs like diclofenac, celecoxib and piroxicam to Erythema Multiforme also reported.

4. Conclusion

This case highlights the importance of considering medication side effects in differential diagnosis of acute rashes as their discontinuation is a key part of treatment. EM in elderly patients, specifically, should prompt detailed history-taking to find the possible triggering agent and stop the culprit drug to avoid future more severe presentations and/or sequelae.

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