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ERYTHEMA MULTIFORME: A CASE REPORT

[1] Sri Devi K [1]Associate Professor, Department of Oral medicine and Radiology
[2] Rama raju [2] Professor ,Department of Oral medicine and Radiology

[1] Chandra Dental College and Hospital,Barabanki, Lucknow.
[2] Karnavati School Of Dentistry, Gandhinagar, Gujarat.

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ABSTRACT
Erythema multiforme (EM) is an acute self limiting, blistering and ulcerative allergic response of the skin and mucous membranes. This condition is usually associated with certain infections mainly herpes, medications and other triggers. It may be present within a wide spectrum of severity. The hallmark of erythema multiforme is target lesion with variable mucous membrane involvement. In erythema multiforme minor, only one mucous membrane is affected and it usually is the oral mucosa. Although many suspected etiologic factors have been reported to cause EM, EM minor is regarded as being commonly triggered by HSV. EM typically affects young individuals mainly 2nd to 4th decades. We report a case of EM in a 10 year old boy which is presented in association with HSV infection..

KEY WORDS:. **Papillion Erythema multiforme, target lesion, herpes simplex virus.**

INTRODUCTION

The term EM includes a wide range of clinical expressions, from exclusive mucous membrane or skin erosions to mucocutaneous lesions (EM minor) and, in its more severe forms, there is serious involvement of mucosal membranes of more than one system and skin (EM major, Steven – Johnson syndrome) or a large area of the total body surface including mucousal surfaces (Toxic Epidermal Necrolysis) with constitutional symptoms and, at times, visceral invovement[1]. It has been claimed that cases of this nature were described earlier in France by Niber & Bazin[2], but the initial description of EM is attributed to Ferdinand von Hebra, who first described EM in 1860 as self limited, mild skin disease characterized by symmetrically distributed lesions, located primarily on the extremities and a tendency for recurrences. The primary lesions were characterized by the abrupt appearance of round red papules, some of which evolved into target lesions. The EM described by von Hebra is sometimes called as EM minor[1,3].

In 1987, the isolated oral manifestations of this disease were recognized as group variants of EM and being called as oral EM[1]. The spectrum of EM comprises EM minor, Steven Johnson Syndrome (EM major) and Toxic epidermal necrolysis (Lyell's) disease. In the current knowledge of EM spectrum, EM minor usually associated or not to Herpes Simplex Virus (HSV) or other infections, can be separated from Steven Johnson Syndrome and Toxic epidermal necrolysis as those frequently are associated with drug exposure[4].

Case report

A 10 year old male patient referred from dermatology unit, attended the Department of Oral Medicine & Radiology, Government Dental College & Hospital, Hyderabad, with a complaint of inability to eat food since 1 week due to blisters and ulcers in the mouth. There was a history of recurrence of similar attacks of blisters and ulcers in the mouth, lips and on the skin for 3 times since 1 year. The lesions were started as blisters, persisted for 2-3 days and ruptured to leave erosions. There was a history of associated fever along with the onset of the lesions. Patient had taken treatment in dermatology unit. There was no significant history of past illness, family and personal histories. There was no history of allergy to drugs or other known substances. Target lesions were found on forehead on the right side **(Fig.1)**, left elbow **(Fig.2),** palms **(Fig.3**) and extensor surfaces of both the knees **(Fig.4).** Left submandibular lymph nodes were palpable, non tender, firm, mobile and 2 in number. Irregular erosions with crustations were seen on both the lips and labial mucosae **(Fig.5).** Erosions were also seen on the soft palate and on the tip of the tongue. Erosion on the soft palate was of 2×2.5 cm in size, showed irregular margins and an inflammatory halo. On the tip of the tongue there was a linear erosion of 1.5×0.5cm in size & it is surrounded by yellowish margin **(Fig.6**). The erosions were tender on palpation, not fixed and not indurated.

Based on the above said findings a diagnosis of erythema multiforme was arrived at and a differential diagnoses of pemphigus vulgaris, bullous lichen planus and behcet's syndrome were considered. Hematological investigations showed positive for HSV1 antibodies. Histopathology showed connective tissue changes as infiltrates of lymphocytes and macrophages in the perivascular spaces and connective tissue papillae. Immunofluorescence was positive for compliment C3 & IgG antibodies.

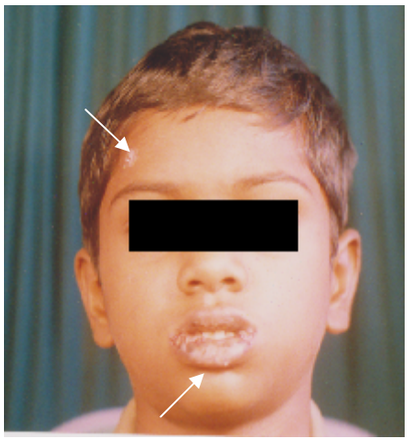

Fig.1 Photograph depicting the lesions on the forehead and lips

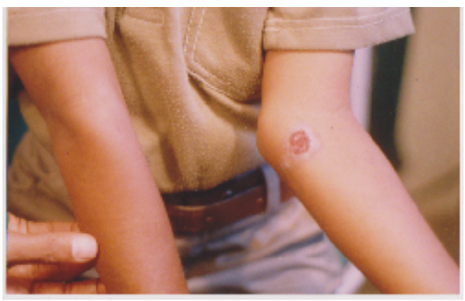

Fig.2. Photograph depicting the lesions on the left elbow.

Fig.3. Photograph depicting the lesions on the palms.

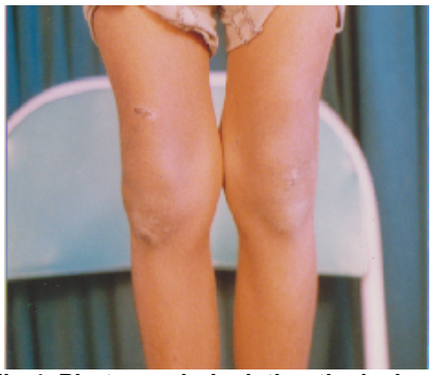

Fig.4. Photograph depicting the lesions on the extensor surfaces of knees

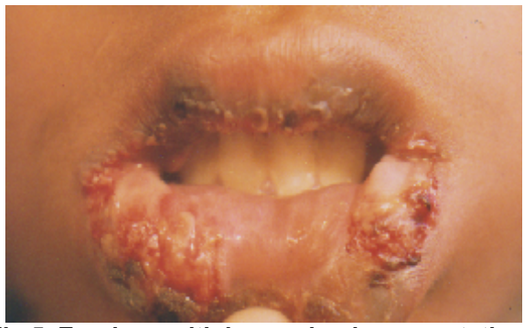

Fig.5. Erosions with hemorrhagic encrustations on the lips.

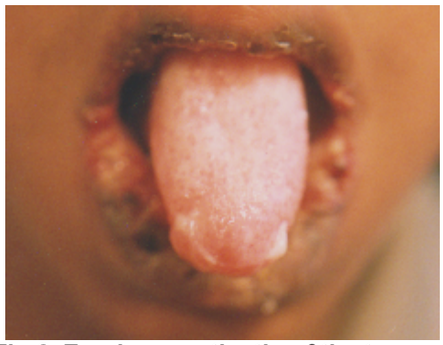

Fig.6. Erosions on the tip of the tongue.

Discussion

EM is an immune mediated disease that may be initiated either by deposition of immune complexes in the superficial microvasculature of skin and mucosa, or cell mediated immunity[5]. The pathogenesis of EM minor may involve an immune complex mediated vasculitis[6]. Kokuba et al[7] stated that the Herpes Associated Erythema Multiforme (HAEM) lesions were positive for interferon γ, a product of antigen activated CD_4 TH1 cells involved in delayed type hypersensitivity reactions[8]. Although some rare cases of EM minor can be idiopathic[1], several etiological factors can be associated with its development. Some medications (principally anticonvulsants, sulfonamides, non steroidal anti inflammatory drugs and antibiotics), food allergy, HSV, HBV and EBV infections, Mycoplasma pneumoniae infections, coccidiodomycosis, candida, histoplasma, yersenia[9], radiation(mainly UV), dermatomyositis, lupus erythematosus, physical agents (koebner phenomenon) and acute alcoholism are mentioned as etiological agents. The herpes associated erythema multiforme (HAEM) is a recurrent disease that can be precipitated by sun exposure and does not progress to Steven Johnson syndrome[10]. Even in the absence of a clear clinical history of Herpes Simplex Virus infection, subclinical HSV is likely the precipitating factor, as evidenced by the polymerase chain reaction (PCR) analysis of HSV[3].

EM is most frequently seen in children and young adults and is rare after age 50. Although most studies indicate prevalence of the masculine gender, others show feminine predilection of 1.5:1[11,12]. The incidence does not show any racial preference[12]. The estimated incidence ranges from 1.1 person in every 1000000 per year in Germany, to 3.7 in USA and up to 5-10 in Sweden[1]. Recurrences occur in 37% of cases, they usually happen in the spring and autumn[13]. Prevelance of oral EM minor varies from 35-65% among patients with skin lesions. However, in patients where EM minor was diagnosed by oral lesions, incidence of skin lesions ranged from 25-33%[2]. 70% of cutaneous recurrent EM minor patients had an oral involvement, comprising multiple large, shallow, extremely painful and debilitating ulcers [13]. The oral lesions have predilection for the vermillion border of the lips and the buccal mucosa, generally sparing the gingiva.

Lesions of EM minor can be persistent (continuous), cyclical (acute and self limiting) or recurrent, the cyclical and recurrent lesions occur mainly in the HAEM[14]. The condition can begin with non specific prodromal symptoms such as headache, malaise and fever. Symptoms last for 3-10 days, after which an inflammatory process yields the pathognomonic target or iris lesion. Target lesion consists of a central bulla or pale clearing area surrounded by edema and bands of erythema[15]. These target lesions typically appear on the cutaneous surfaces, including palms, soles and extremities. The face, neck and trunk are less commonly involved. When the mucosal surfaces are affected, the oral mucous membrane is most commonly affected[11,12]. Hemorrhagic crusting of the lips and ulceration mainly of the non keratinized mucosa characterize oral lesions. When it affects the lips, it results in erosions or hemorrhagic crusts, with pathognomonic blood stained crusting of erosions on swollen lips, hindering the phonation, feeding and limiting the oral movement[1]. The intraoral lesions mainly attack the anterior aspect, the tongue and buccal mucosa being the more involved places[16]. Although any place can be affected, the hard palate[16] and gingiva are usually spared[1,2]. Other mucous membranes that can be affected mainly in HAEM cases include eyes, nose, genetalia, esophagus and respiratory tract[12]. The ocular lesions are of particular concern because they can result in scarring and progressive blindness[1].

Although the histopathology is not specific, two major histologic patterns have been described: an epidermal pattern characterized by lichenoid vasculitis and intraepidermal vesicles, and a dermal pattern characterized by lymphocytic vasculitis and subepidermal vesiculation[15,17]. Oral lesions are often necrosed by the time of biopsy and may show secondary inflammation from recurring trauma or from contact with the oral flora. The necrosed keratinocytes are also found in fixed drug eruption, acute graft versus host disease, radiation mucositis and some lichenoid reactions.

The differential diagnoses include pemphigus vulgaris, bullous lichen planus, mucous membrane pemphigoid and oral primary HSV infection. Biopsies must be assessed by means of routine hematoxylin and eosin staining, to exclude any pathology with similar clinical pattern but a specific histopathological one. In questionable cases, a standard direct Immunofluorescence can be performed. Direct and indirect Immunofluorescence studies are not usually useful in the diagnosis, but deposits of IgM and C3 in the walls of superficial blood vessels can usually be identified. Granular deposits of IgM, C3 and fibrinogen may also be present along the basement membrane. Circulating immune complexes are often demonstrated with a monoclonal rheumatoid fraction assay or a C1q binding radioassay. Before any therapy is prescribed, possible underlying causes, such as medication, diet, infections or systemic diseases should be determined and eliminated[18]. Mild cases of oral EM may be treated with supportive measures including topical anesthetic mouthwashes and soft, liquid diet. Moderate to severe oral EM may be treated with a short course of systemic corticosteroids. An initial dose of 30-50mg/day prednisone or methylprednisone followed by tapering the dose is considered to shorten the healing time, particularly when started early in the course of the disease. Higher doses of steroids are necessary for severe cases[15]. The prophylactic and therapeutic use of antiherpes drugs like acyclovir, valacyclovir and famciclovir, in cases of HAEM is a common practice[8]. When HSV lesions precede the

target lesions, an intermittent therapy with 200mg twice a day for five days would prevent or minimize the symptoms of erythema multiforme[18,19]. In recurrent EM associated with HSV, supportive treatment using 400mg acyclovir twice a day for six months has also been effective in preventing the recuurence[1,18]. Patients with severe cases of recurrent EM have been treated with dapsone, levamisole or thalidomide[15].

In EM minor, the lesions ultimately subside within 2-3 weeks without scarring. The EM major (SJS, TEN) has a mortality of less than 5%. It usually has a more protracted course than EM minor; clearing may require 3-6 weeks. Erythema multiforme is a self limiting, blistering and ulcerative condition characterized by targetoid skin lesions and/or ulcerative oral lesions. Still some more endeavor and zest is needed for further insight into the etiopathogenesis, management and prevention of recurrences in erythema multiforme.

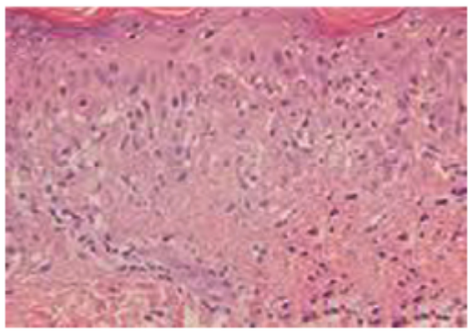

Fig.7. Photomicrograph of the lesion

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Corresponding Author

Dr. K. Sridevi, M.D.S.
Oral Medicine & Radiology
Associate Professor
H NO: 6-5-19/A
Vegiwari Street; Near Old Busstand
Kovvur; West Godavari Dt
Andhra Pradesh
Mobile No: 9885248434
Email ID: srigivi123@gmail.com