"Drug Induced Erythema Multiforme" – A Review

Dr. Sudakshina Mukherjee, Dr. N. Aravindha Babu., Dr. L.Malathy, Dr. N.Anitha

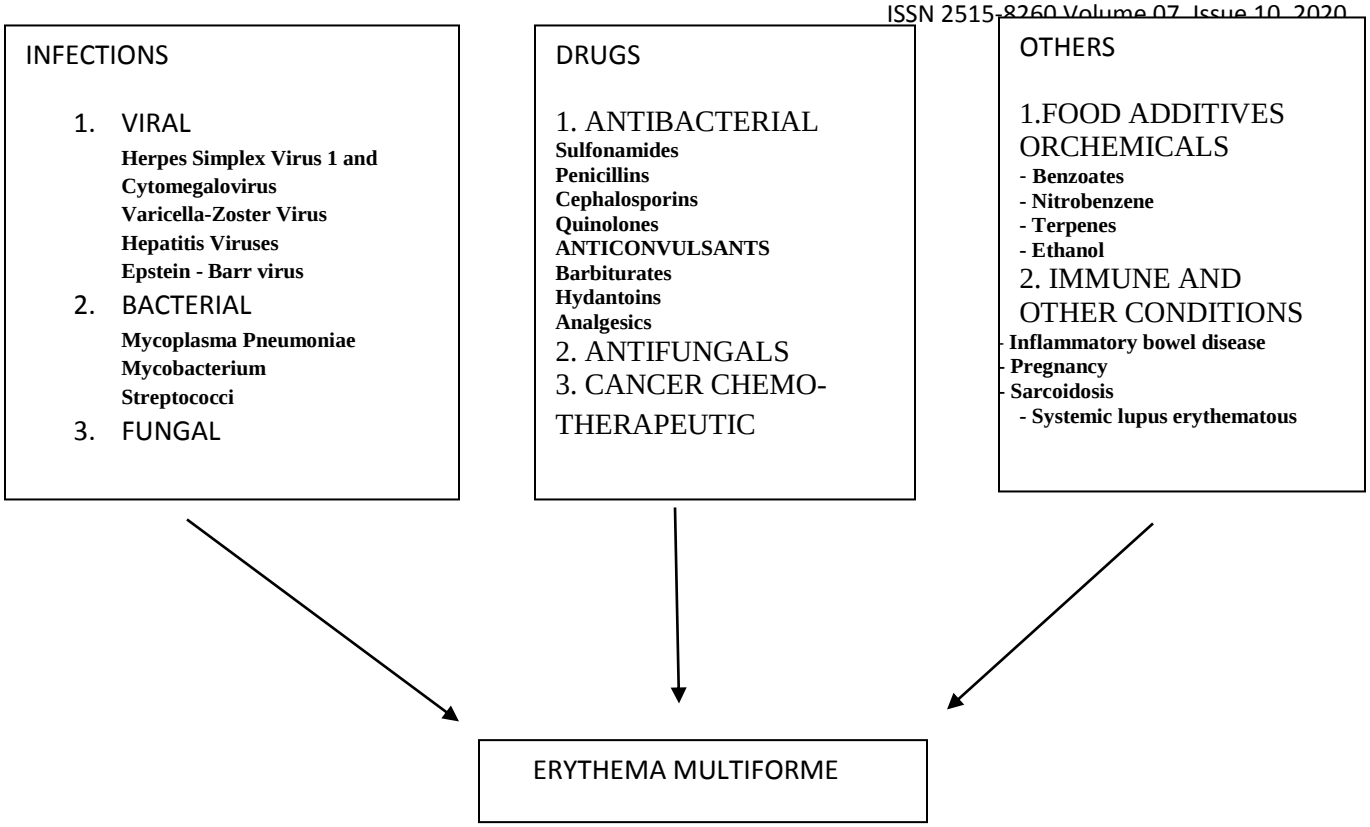
Post graduate student. Department of Oral pathology and Microbiology
Sree Balaji Dental College and Hospital and Research
Bharath Institute of Higher Education and Research

ABSTRACT: ***Erythema Multiforme (EM) is an uncommon, acute inflammatory reactive mucocutaneous disorder. It's a hypersensitivity reaction to different antigenic stimuli, most common being infection followed by drugs. It occurs predominantly in younger age group. Recurrence in EM can be seen especially secondary to HSV infection. Erythema multiforme is manifested clinically as classical cutaneous target like lesions and mucosal bullae or erosions. Within the total affected patients 70% of them suffer from mucosal involvement though mucosal involvement separately is comparatively rare. Manifestations of EM can be varying and may pose a diagnostic dilemma because infections (particularly herpes simplex and mycoplasma pneumoniae) and drugs seem to predispose towards development of EM.***

KEYWORDS: erythema multiforme, Stevens and Johnson, target lesion, bilateral conjunctivitis

INTRODUCTION:

Bateman and Bulkley in the year of 1817 first recognized EM, But in the year 1846, the first American case "Herpes Iris." was reported. Later, in 1866 under the term "erythema exsudativum multiforme" first characteristic morphological feature of this particular eruptions was described by Hebra[1] along with its cause which was due to internal or systemic origin and not for any local etiology [2]. Stevens and Johnson, [3] in 1922, reported EM with predominant involvement of the oral and conjunctival mucous membranes as "a new eruptive fever associated with stomatitis and ophthalmia." On systemic drug administration severe reactions are manifested which characterizes like EM, and Steven Johnson syndrome. Often these reactions can also be characterized as either anaphylactic stomatitis or like intraoral fixed drug eruptions, sometimes may appear as drug induced lichenoid reactions and pemphigoid–like drug reactions [4]. It is manifested as skin eruption, with or without oral or other mucous membrane lesions [5-7]. This can be activated by chemicals, intake of certain drugs or because of various infections [Table/Fig-1], specifically viral infection like herpes simplex virus (HSV), [5] which has been detected in up to 70% of EM cases [7]. Based on severity and number of mucosal sites involved, EM has been classified into EM Major and EM minor [8]. Oral EM typically characterized by mucosal ulcerations mostly without any skin lesions. It has been reported that even if the primary attacks of oral EM are confined to the oral mucosa the subsequent attacks can produce more severe forms of EM involving the skin and thus it becomes important to detect and distinguish them from other ulcerative disorders involving oral cavity for early management and proper follow-up [8-11]



AETIOLOGY & PATHOGENESIS

The aetiology and pathogenesis of EM is unclear in most patients, but appears to be an immunological hypersensitivity reaction with the CD8+ T lymphocytes, in epithelium, inducing apoptosis of scattered keratinocytes and leading to satellite cell necrosis [13]. Various exogenous factors trigger an immunological reaction that appears as a sub and intra-epithelial vesiculation. A genetic predisposition to EM may be present, along with associations of recurrent EM with HLA-B15 (B62), HLA-B35, HLA-A33, HLA-DR53 and HLADQB1* 0301. HLA DQ3 has been proven to be especially associated with recurrent EM and should be a helpful marker for distinguishing HAEM (herpes-associated EM) from other diseases with EM-like lesions. Patients with severe mucosal involvement may have the rare HLA allele DQB1*0402 [14] Thus viral infections tends to trigger EM minor or major but drug ingestion tends to trigger more severe SJS or Toxic Epidermal Necrolysis (TEN) [15].The lesions due to drug-associated EM when compared with herpes associated EM test positive for tumor necrosis factor α and not interferon-γ as the later thus suggesting a varying mechanism [16]

CLINICAL MANIFESTATIONS:

EM is a self limiting disease that usually has mild or no prodromal symptoms [17] .Patients may experience itching and burning at the site of the eruption [18] . The individual lesions begin acutely as numerous sharply demarcated red or pink macules that then become papular [17,19] with crusting or blistering sometimes occurs in the center of the lesions. The characteristic "target" or "iris" lesion generally has a round shape with three concentric zones namely: a central dusky or darker red area, a paler pink or edematous zone, and a peripheral red ring but in some target lesions mainly two zones can be seen such as the dusky or darker red centre and a pink or lighter red border [17,13].Target lesions may not be vivid until several days after the onset, so when lesions of various morphology are clinically present, the name erythema "multiforme" [24] is given. The skin lesions of EM usually appear symmetrically on the distal extremities and progress proximally [25] Lesions on the dorsal surfaces of the hands and extensor aspects of the extremities are most characteristic [19]. Palms and soles also may be involved [18]. Mucosal lesions may occur but usually are limited to the oral cavity [13]. EM resolves spontaneously in three to five weeks without sequelae, but it may recur [16]. Clinical variants of EM described in [Table-2]

[TABLE-2]

VARIANTS	**MANIFESTATION**
EM minor	Characteristic target lesions seen, atypical target lesions which is raised, mucous membrane involvement is minimal and even if present can be seen only at 1 site (mostly in the mouth). Oral lesions can range from mild to severe erythema, erosions and ulcers. Occasionally the oral mucosa can be affected. Body surface area affected rate is < 10%
VARIANTS	**MANIFESTATION**
EM major	Cutaneous lesions and minimum 2 mucosal sites (typically oral mucosa)are affected. Rate of affected body surface area< 10%. Symmetrically distributed typical or atypical target lesions, raised lesions or both. Oral lesions usually widespread and severe.
Stevens-Johnson syndrome	Main difference from EM major is based on the typology and location of lesions and the presence of systemic symptoms. Rate of affected body surface area < 10%. Atypical flat target lesions and macules appear primarily instead of classic target lesions. Generally widespread rather than involving only the acral areas. Involvement of mucosal sites can be multiple, accompanied with scarring of the mucosal lesions. Prodromal flu-like systemic symptoms also common.
Overlapping Stevens-Johnson syndrome and toxic epidermal necrolysis	No typical targets; flat atypical targets are present. Up to 10%–30% of the body surface area affected. Prodromal flu-like systemic symptoms common.
Toxic epidermal necrolysis	Presence of spots characterizes epidermal detachment of > 30% of the body surface and widespread purpuric macules or flat atypical targets. No spots relate to the epidermal detachment of > 10% of the body surface, large epidermal sheets and no macules or target lesions.

Drug related erythema multiforme	Typically involvement of oral mucosa, lips and occurence of bulbar conjunctivae can be seen. Initially bullae rupture to give rise to haemorrhagic pseudo membrane of the lips and wide spread superficial oral ulcerations.
Drug related Toxic epidermal necrolysis	Clinically Toxic epidermal necrolysis (Lyell syndrome) is characterised by widespread mucocutaneous epidermolysis often preceded by a macular or maculopapular exanthema and enanthema (Lyell, 1979; Rasmussen et al, 1989). Intraoral examination reveals extensive painful blisters and ulceration on all mucosal surfaces. Toxic epidermolysis may be associated with antimicrobials (sulphonamides and thiacetazone), analgesics (phenazones). antiepileptics, allopurinol, chlormezanone, rifampicin, fluconazole and vancomycin.

MUCOSAL MANIFESTATIONS: It is characterized by episodic, recurrent bullae and erosions over lips, on both cutaneous and mucosal sides [figure-1], non-attached gingivae, and the ventral side of the tongue. Generally hard palate as well as the attached gingivae is spared.[21] On the cutaneous part of the lips, identifiable target lesions may be discernible. The lesions rarely spreads upto the throat, larynx, and even the trachea and bronchi interfering with speech, mastication, and swallowing producing considerable morbidity. Eye involvement begins with pain and bilateral conjunctivitis [figure-2] in which vesicles and erosions can occur with lacrimation and photophobia.[22] Other mucosal surfaces like nasal, anogenital and urethral mucosae may be inflamed and eroded. Genital lesions are painful and can cause in urinary retention. Scarring sequelae from ocular and pharyngeal involvement can cause morbidity.[23]

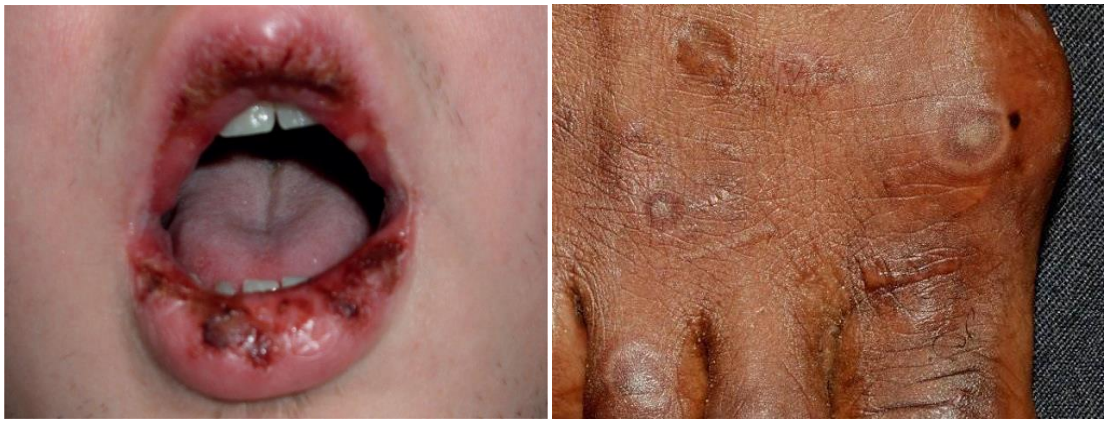


FIGURE-1

FIGURE- 2; **Conjunctival congestion**

DIFFERENTIAL DIAGNOSIS: Differential diagnosis can be shortlisted on the basis of lesions which involve mainly the oral regions like what is seen in case of infections like herpes, certain autoimmune vesiculobullous lesions such as pemphigus vulgaris or bullous pemphigoid and others which include different patterns of drug reactions. Patterns of drug reactions like lichenoid drug reactions, pemphigoid-like drug reactions are often easily differentiated supporting the clinical patterns as above mentioned. Anaphylactic stomatitis often shows urticarial skin reactions with other signs and symptoms of anaphylaxis by which we can differentiate the lesions. In mucosal fixed drug eruptions the lesions are confined within the local areas of oral mucosa.

LABORATORY FINDINGS: Due to inflammation, C-Reactive protein (CRP) may be positive and the erythrocyte sedimentation rate is elevated. In some cases certain markers like the HSV antibody titer, Mycoplasma antibody titer and antistreptolysin O or ASO titer are raised. In cases involving bacterial infection, there is an increase in neutrophils [1] .The diagnosis is generally supported by biopsy of peri-lesional tissue and excluding other causes.

HISTOPATHOLOGY: Biopsy is advised in early vesicular lesions of EM not in ulcerated ones since histopathologic appearances are nonspecific and non-diagnostic [8].Main histological findings are describes below in [Table-3]

Classification	Main Histological Findings
Epidermal	lymphocytic infiltration and ballooning degeneration in the dermo-epidermal junction characterizes the early stage of the disease. As it progresses, CD8+ lymphocytes infiltration into the epidermis can be noticed, which results in keratinocyte necrosis and subepidermal blistering. There appears to be reduction of epidermal Langerhans cells and ICAM-1 overexpression on keratinocytes
Dermal	Perivascular monocytic infiltration in the upper dermis with consequent edema in the dermal papilla is manifested when EM is associated with some dermal changes
Mixed	Epidermal changes seen as vacuolar degeneration of the basal layer, satellite cell necrosis with dermal

	changes like perivascular lymphocytic infiltration.

[Table-3]

TREATMENT: No single specific treatment modality is available despite the advancement in the diagnosis. There should be identification and withdrawal of the causative agent/drug along with supportive care. Mild cases of oral EM are treated mainly with palliative measures including application of topical anesthetic mouthwashes and liquid and soft diet. To treat moderate to severe cases of oral EM a short course of systemic corticosteroids can be given in patients without any significant contraindications to their use. Systemic corticosteroids should only be used by clinicians familiar with the side effects, and, in each case, potential benefits should be carefully weighed and the dose should be tapered over 2 to 3 weeks. Recently immunomodulating/immunosuppressive drugs (Dapsone, Azathioprine, Levamisole) are showing promising results in suppression of disease progression [20]

CONCLUSION: Drug induced Oral EM is considered to be a rare and less described variant of Erythema Multiformae. HSV infections mostly responsible for triggering EM rather than the systemic administration of drugs which in turn result in adverse reactions. Even though it has been observed that the primary attack of drug induced EM is confined to the oral mucosa the subsequent attack can produce more severe forms of EM (EM minor, EM major) involving their skin. It is important for oral pathologists and general dentists to have a clear knowledge about the differential diagnosis related to EM in order to differentiate from other vesicullobullous lesions from drug induced EM thus helping in prompt management and proper follow-up.

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