Drug Induced Erythema Multiforme: Two Case Series with Review of Literature

ABSTRACT
Erythema multiforme, (EM) an uncommon, acute inflammatory reactive mucocutaneous disorder and primary allergies confined to the oral mucosa. However the subsequent attacks can produce more severe forms of EM involving the skin. Manifestations of EM are varied and present a diagnostic dilemma because infections (particularly herpes simplex and mycoplasma pneumoniae) and drugs seem to predispose towards development of EM. We report two cases of erythema multiforme in which drugs (Diclofenac sodium & Amoxycilline) seems to be precipitating factor. In addition, the article reviews various aspects of EM as relevant to dental practice and highlight the associated potential etiologic agents, pathogenic mechanisms and therapies.

CASE REPORTS
CASE 1: A 23-year-old female patient reported to the dental OPD with complaints of extensive painful ulcers and hemorrhagic crusts on the lips. She reported having painful oral ulceration and difficulty in eating. There is no significant family history except that she gave history of fever and common cold two weeks back for which she took azithromycin and diclofenac sodium, subsequently she developed irregular ulceration and hemorrhagic crust on the upper lip [Table/Fig-1]. On examination The upper lip was showing irregular ulcerations with yellow base and both right & left buccal mucosa showing irregular ulcerations [Table/Fig-2a,b]. Bilateral submandibular lymph nodes were enlarged and tender. A diagnostically significant finding was presence of multiple typical target lesions on the dorsal and ventral surface of feet and erythematous lesions on the palm and planter surface of the hands [Table/Fig-3a,b,4a,b]. The Patient was advised to discontinue the medication. Sudden onset of lesions, positive drug history associated with aggressive clinical features lead us to the diagnosis of erythema multiforme.

CASE 2: A 35-year-old female reported to the dental outpatient Department with chief complaint of painful ulceration of the oral cavity for the past five days. Medical and family history was not significant. She gave history of swelling in relation with maxillary left central incisor for which she took amoxycilline & diclofenac Sodium few weeks back, within days she developed oral ulcerations. She gave a history of multiple vesicles of the oral mucosa on buccal and labial mucosa which ruptured to form painful ulcerations. After two days she developed ulcerations of lips [Table/Fig-5,6]. Patient was unable to eat solid food and was on liquid diet for the last two days. She had stopped medicines after developing vesicles. An oral examination showed ulcerations over the upper and lower lip [Table/Fig-5,6]. Intra orally white coating over the tongue and palate, & ulcerations over the right buccal mucosa were noted [Table/Fig-7]. Routine hematological investigations were advised and found within normal range. ESR was 25 mm in first hour by Westergreen’s method. Investigations for hepatitis B and C, and HIV were negative.

We were able to establish a temporal relationship between the drug intake and occurrence of the oral mucosal lesions. The oral ulcerations in our cases started within a few days of the drug intake and were resolved upon cessation of the drug. Erythema multiforme is usually triggered by herpes simplex infections, but rarely by drug intake.

REVIEW OF LITERATURE
Adverse reaction to systemic drug administration can be manifested as erythema multiforme, Steven Johnson syndrome, anaphylactic stomatitis, intraoral fixed drug eruptions, lichenoid drug reactions, and pemphigoid–like drug reactions [1]. It is manifested as skin eruption, with or without oral or other mucous membrane lesions [2-4] It can be triggered by chemicals, drug intake or several infections [Table/Fig-8], in particular herpes simplex virus (HSV) infection.2 which has been identified in up to 70% of erythema multiforme cases [5]. Based on severity and number of mucosal sites involved, EM has been classified into EM Major and EM minor.6 Oral EM shows typical mucosal ulcerations without any skin lesions. It has been
CD4+ cells respond to viral antigens with production of interferon-γ, initiating an inflammatory cascade. HSV genes within DNA fragments have been well studied and is consistent with a delayed-type hypersensitivity reaction [17,18]. The pathogenesis of herpes-associated erythema multiforme 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 [6]. A range of exogenous factors triggers an immunologically related reaction which appears as a sub and intra-epithelial vesiculation. There may be a genetic predisposition to EM, 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 related to recurrent EM and may be a helpful marker for distinguishing HAEM (herpes-associated EM) from other diseases with EM-like lesions. Patients with extensive mucosal involvement may have the rare HLA allele DQB1*0402.15 Thus viral infections appear to trigger EM minor or major but drug ingestion tends to trigger more severe SJS or Toxic Epidermal Necrolysis (TEN) [16].

Clinical Presentations
Erythema multiforme is a self limiting disease that usually has mild or no prodromal symptoms [19]. Patients may experience itching and burning at the site of the eruption [20]. The individual lesions begin acutely as numerous sharply demarcated red or pink macules that then become papular [19,21] with crusting or blistering sometimes occurs in the center of the lesions. The characteristic “target” or “iris” lesion has a regular round shape with three concentric zones: a central dusky or darker red area, a paler pink or edematous zone, and a peripheral red ring. Some target lesions have only two zones, the dusky or darker red centre and a pink or lighter red border [19,6].

Target lesions may not be apparent until several days after the onset, when lesions of various morphology clinically are present, hence the name erythema “multiforme” [22]. The skin lesions of erythema multiforme usually appear symmetrically on the distal extremities and progress proximally [23]. Lesions on the dorsal surfaces of the hands and extensor aspects of the extremities are most characteristic [21]. Palms and soles also may be involved [20] Mucosal lesions may occur but usually are limited to the oral cavity [6]. Erythema multiforme resolves spontaneously in three to five weeks without sequelae, but it may recur [17]. Clinical variants of Erythema multiforme described in Table/Fig-9.

DIFFERENTIAL DIAGNOSIS
Various lesions are to be considered which are confined to the oral region are herpes, autoimmune vesiculobullous lesions such as pemphigus vulgaris or bullous pemphigoid and other patterns of drug reactions. Our cases did not have any gingival ulceration. Extensive irregular ulcerations in the lining non keratinized mucosa of the oral region are herpes, autoimmune vesiculobullous lesions such as pemphigus vulgaris or bullous pemphigoid and other patterns of drug reactions. Our cases did not have any gingival ulceration. Extensive irregular ulcerations in the lining non keratinized mucosa of the oral region are herpes, autoimmune vesiculobullous lesions such as pemphigus vulgaris or bullous pemphigoid and other patterns of drug reactions. Our cases did not have any gingival ulceration. 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Laboratory Findings: Because of inflammation, C-Reactive protein (CRP) may be positive and the erythrocyte sedimentation rate is elevated. The herpes simplex virus antibody titer, Mycoplasma antibody titer and antistreptolysin O (ASO) titer may be elevated in some cases. In cases involving bacterial infection, there is an

Drug-associated erythema multiforme lesions test positive for tumor necrosis factor α and not interferon-γ as in herpes associated erythema multiforme lesions, suggesting a varying mechanism [17]. The pathogenesis of herpes-associated erythema multiforme has been well studied and is consistent with a delayed-type hypersensitivity reaction [17,18]. HSV genes within DNA fragments are expressed on keratinocytes, leading to the recruitment of HSV-specific CD4+ TH1 cells (helper T cells involved in cell-mediated immunity). The CD4+ cells respond to viral antigens with production of interferon-γ, initiating an inflammatory cascade [17].
Direct/Indirect immunofluorescence reveals antibodies

Drugs

Other

ANTIBACTERIAL
- Sulfonamides
- Penicillins
- Cephalosporins
- Quinolones
- Chloramphenicol
- Metronidazole

FOOD ADDITIVES OR CHEMICALS
- Benzocaine
- Nitrobenzene
- Terpenes
- Ethanol

IMMUNE AND OTHER CONDITIONS
- Inflammatory bowel disease
- Pregnancy
- Sarcoidosis
- Systemic lupus erythematos

Histopathology:

[Table/Fig-11]: Histopathological Classification

Infections | Drugs | Others
---|---|---
Erythema multiforme minor | Typical target lesions, raised atypical target lesions, minimal mucous membrane involvement and, when present, at only 1 site (most commonly the mouth). |oral lesions; mild to severe erythema, erosions and ulcers. Occasionally may affect only the oral mucosa. < 10% of the body surface area is affected.

Erythema multiforme major | Cutaneous lesions and at least 2 mucosal sites (typically oral mucosal affected). < 10% of the body surface area involved. Symmetrically distributed typical target lesions or atypical, raised target lesions or both. Oral lesions usually widespread and severe.

Stevens-Johnson syndrome | Main difference from erythema multiforme major is based on the typology and location of lesions and the presence of systemic symptoms. < 10% of the body surface area is involved. Primarily atypical flat target lesions and macules rather than classic target lesions. Generally widespread rather than involving only the acral areas. Multiple mucosal sites involved, with scarring of the mucosal lesions. Proctodermal 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. Proctodermal flu-like systemic symptoms common.

Toxic epidermal necrolysis | When spots are present, characterized by epidermal detachment of > 30% of the body surface and widespread purpuric macules or flat atypical targets. In the absence of spots, characterized by epidermal detachment > 10% of the body surface, large epidermal sheet and no macules or target lesions.

Drug related erythema multiforme | Typically affect the oral mucosa, the lips and bulbar conjunctivae. Initially bullae rupture to give rise to haemorrhagic pseudo membrane of the lips and widespread superficial oral ulcerations.

Drug related Toxic epidermal necrolysis | Toxic epidermal necrolysis (Lyell syndrome) is clinically characterised by extensive mucocutaneous epidermolysis preceded by a macular or maculopapular exanthema and exanthema (Lyell, 1979; Rasmussen et al, 1989). Intranasally there is widespread painful blistering and ulceration of all mucosal mucosal surfaces. Toxic epidermolysis may be associated with antimicrobials (sulphonamides and thiazides), anaphylaxis (phenazone), antineoplastic, atropinol, chlorozone, rifampicin, fluconazole and vancomycin.

Increase in neutrophils [12]. The diagnosis is usually supported by peri-lesional tissue biopsy and exclusion of other causes.

Histopathology: Biopsy is advised in early vesicular lesions of erythema multiforme not in ulcerated ones since histopathologic appearances are nonspecific and non-diagnostic [7]. In the early stages of epidermal EM, there is lymphocytic infiltration into the dermo-epidermal junction and vacuolar degeneration of basal cells. As the disease progresses, lymphocytes (CD8+T cells) infiltrate into the epidermis and necrosis of epidermal cells and subepidermal blistering are found. Histologically it is classified into three i.e epidermal, dermal and mixed. [Table/Fig-11] [12]. Histological examination and immunostaining often shows moderate increase in neutrophils [12]. The diagnosis is usually supported by peri-lesional tissue biopsy and exclusion of other causes.

Infected | Drugs | Others
---|---|---
VIRAL | Herpes Simplex Virus 1 and 2 |Cytopneumovirus Varicella-Zoster Virus Hepatitis Viruses Epstein-Barr Virus

BACTERIAL | Mycoplasma Pneumoniae Mycobacterium Streptococci

FUNGAL INFECTIONS: PARASITES

[Table/Fig-6]: Causes of Erythema Multiformae

Disorder | Different from Erythema Multiforme
---|---
Urticaria | Itching is more severe. Each lesion usually disappears within 24 hours. Dermographism rubrum occurs.

Systemic Lupus Erythematosus | Systemic symptoms occur (renal, articular etc) Laboratory findings of antinuclear antibodies, etc. EM sometimes occur in SLE

Bullous Pemphigoid | Direct/Indirect immunofluorescence reveals antibodies against basement membrane.

Acute Herpetiform stomatitis | Ulcers are smaller with regular borders.

[Table/Fig-10]: Differential diagnosis

Classification | Main Histological Findings
---|---
Epidermal | In the early stage, lymphocytic infiltration and ballooning degeneration in the dermo-epidermal junction. As the disease progresses, infiltration of CD8+ lymphocytes into the epidermis, resulting in keratinocyte necrosis and subepidermal blistering. Decrease of epidermal Langerhans cells and overexpression of ICAM-1 on keratinocytes.

Dermal | Perivascular monocytic infiltration in the upper dermis, edema in the dermal papilla. It is now said that erythema multiforme is always accompanied by at least some change in the epidermis.

Mixed | Epidermal changes (vascular degeneration of the basal layer, satellite cell necrosis); dermal changes (perivascular lymphocytic infiltration).

For CASE 1-Oral corticosteroid (methylprednisolone at the dose of 32 mg/ day) was started. Within 5 days, all the mucosal lesions healed and methylprednisolone was stopped after tapering over next 7 days. Mouthwashes consisting of local anaesthetics and antiseptics were added to aid in oral fluid intake.

For CASE 2- Patient was treated with corticosteroid twice a day for 3 days followed by tapering dose for 10 days and local application of topical anesthetic gel for pain relief. The lesions completely regressed after 10 to 12 days in both cases.

SUMMARY AND CONCLUSION

Drug induced Oral EM is a rare and less described variant of Erythema Multiformae. EM is often triggered by HSV infections and rarely by adverse drug reactions. Even though 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 differentiate from other vesiculobullous lesions from drug induced EM for prompt management and proper follow-up.

REFERENCES