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Dentistry

DRUG INDUCED ERYTHEMA MULTIFORME IN POST COVID19: A REVIEW AND A RARE CASE REPORT

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ABSTRACT Erythema multiforme is an intriguing dermatological condition with oral manifestations. Mycoplasma pneumoniae and herpes simplex appear to increase the risk of developing EM. 24-year-old male patient reported to OPD of extensive pain and bleeding lesions in the mouth. Reguero et al., for instance, described a 95-year-old female patient who developed EM lesions two days after being released from the hospital after being infected with SARS-CoV-2 and receiving hydroxychloroquine for ten days; the authors did not link the EM to medication in this instance. It has been noted that EM and EM-like eruptions are mostly linked to SARS-CoV-2 infection or, much less frequently, are brought on by the illness's treatment. The pathophysiological mechanism of these skin eruptions may be a hypersensitivity reaction driven by skin-resident lymphocytes targeting SARS-CoV-2 antigen, as has been described for EM linked to other infections. Specifically, CD8+ T lymphocytes cause satellite cell necrosis by causing scattered keratinocytes to undergo apoptosis. From this, it can be inferred that COVID 19 infection has an essential correlation with such mucocutaneous lesions. Therefore, it is mandatory for the clinician to take a proper history of the infection with COVID19 and further aggressive treatment planning can be done accordingly.

KEYWORDS : Erythema Multiforme, Drug Induced, Covid19

INTRODUCTION:

Erythema multiforme (EM) is an interesting dermatologic disease which has oral manifestations. EM is clinically characterized by a "minor" form and a "major" form. It presents a diagnostic dilemma because the oral cavity has the ability to produce varied manifestations. Infections (particularly herpes simplex and mycoplasma pneumonia) and drugs seem to predispose toward the development of EM. The range of possible aetiologies for oral disease is immense.[1]

It is a skin disease characterized by the appearance, usually on the extremities but often also occurring in other skin areas, of reddish, annular macules, which later become papules, sometimes coalescing to plaques. Often, the earliest EM lesions have a target appearance, with a central portion that can appear as a dusky area, surrounded by a dark red inflammatory zone and another lighter ring on the extreme periphery.[2]

Adverse drug-related skin reactions that have a frequency above 1% are urticaria, angioedema, photosensitivity, fixed drug eruptions, erythema multiforme (EM), Stevens–Johnson syndrome, and toxic epidermal necrolysis.[3]

It is a potentially serious immune-mediated, hypersensitivity reaction of the skin, often recognized by its pathognomonic targetoid lesions. It is most commonly triggered by infections such as herpes simplex virus (HSV), *Mycoplasma pneumoniae*, Epstein-Barr virus (EBV), and HIV and less commonly by reaction to medications or from immunosuppression.[4]

More than half the cases have no known cause, while half are caused by medications, infections, immunotherapy, or illnesses. Culprit drugs are antibiotics such as β-lactams (penicillin, cephalosporins) and non-β lactams (clindamycin, trimethoprim–sulfamethoxazole, ethambutol, tetracycline-like drugs, clindamycin, rifampicin), anticonvulsants (carbamazepine, phenytoin, phenylbutazone, phenothiazine-like drugs, barbiturates), allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs), oral antidiabetics (Sulfonamides, chlorpropamide, tolbutamide), codeine, furosemide, gold, and protease inhibitors.[3]

Stevens–Johnson syndrome is a rare, immune-complex mediated disease involving the skin and the mucous membranes. The syndrome was first described in 1922 by Albert Mason Stevens and Frank Chambliss Johnson. It is considered as a minor form of toxic epidermal necrolysis, with less than 10% body surface area evidencing detachment.[5]

The term epidermolysis bullosa (EB) refers to a group of inherited blistering skin diseases, some of which are among the most severe conditions in dermatology. The hallmark of all forms of EB is fragility of the skin such that it blisters following relatively minor trauma. In many cases, it first presents at, or shortly after, birth. The mildest and most common form of EB is called EB simplex (Irvine, 2005). Individuals with EB simplex typically has blisters on their feet from rubbing footwear, particularly during the summer when heat and sweating exacerbate the problem. Although usually limited in extent, EB simplex can be extremely painful and debilitating. The junctional and dystrophic forms of EB are generally more severe. Junctional EB can result in very extensive loss of the epidermis, with most such cases failing to survive beyond infancy (McGowan and Marinkovich, 2002). The increased morbidity occurs as a result of overwhelming skin and mucous membrane fragility, which leads to susceptibility to infection and failure to thrive. Dystrophic EB varies in its severity but in all cases, blisters are followed by scarring of the skin or mucous membranes. In some cases, particularly more severely affected adults, there is an increased risk of developing skin malignancy, notably squamous cell carcinoma.[6]

Case Description:

A 24-year-old male patient reported to OPD of department of Oral Medicine and Radiology with extensive pain and bleeding lesions in mouth on right and left cheek, right and left side of tongue and corner of lips of both sides enabling patient to open his mouth in the last 2 days. The lesion started with redness along with burning sensation. Later bleeding lesion appeared at all sites. Patient also complained difficulty to maintain oral hygiene due to pain. Patient had a history of diarrhea 5 days before coming to department for which he had taken antibiotic combination of ofloxacin 200 mg and ornidazole 500mg twice daily for 3 days after which there was occurrence of the ulcer. Patient applied combination of chlorhexidine gluconate and metronidazole gel along with benzocaine gel over the ulcer. There was no complaint of fever, itchiness, or ocular involvement.

Patient also reported the earlier history of similar solitary lesions on buccal mucosa after administration of antibiotics several times. These lesions were reported to be of mild form and were painless and patient did not report any discomfort along with it. The lesions were self-healing within 2-3 days after stoppage of administration of antibiotics. This was followed by inability to open mouth because of bleeding and ulcer. Patient also was unable to talk, chew food or eat solid food and was on liquid diet for 2 days. At this time patient visited to our institute for expert opinion.

On physical examination, lateral border of tongue, bilateral cheek mucosa and angle of mouth had red irregular ulcerations. Patient also had crestations on the angle of mouth. The upper lip showed black irregular crestations. Pharyngeal and laryngeal examination was normal. No neck nodes were palpable. Other systemic examination was normal. Patient gave the history of COVID-19.

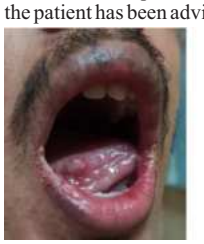
Family history showed similar allergic mucosal ulcerations after consumption of sulfa drugs on the maternal side of patient. Blood tests were performed which showed increased Erythrocyte count, mean Corpuscular Hb count, absolute Neutrophils count, Absolute Lymphocyte Count (pathologic remark as neutrophilic leucocytosis) and the patient was advised to avoid drugs such as, Sulfa, NSAIDS, Quinolones/ Oflox / Ciplox, Tetracyclines/ Doxycycline, Dilantin.

He was advised application of acyclovir cream to be applied over angle of mouth twice a day for 3 days along with benzydamine mouthwash to be kept in mouth for 1 minute, rinsed and then spit out. Repeat this 15-to-20-minute prior every meal for 5 days.

Patient consulted a dermatologist 5 days later where he was prescribed methylprednisolone tablets to be taken after meals twice a day for 5 days along with dexlansoprazole MR capsules 30 mg before meals once a day for 5 days. Pt was also given lidocaine oral topical solution to be used twice a day along with levocetirizine dihydrochloride and montelukast sodium tablets once a day before meals for 5 days and azithromycin tablets 500 mg once a day after meals for 5 days.

On the next visit to the dermatologist, continuation of methylprednisolone tablets to be taken after meals once a day for 5 days and along with-it cyclosporine capsule 100 mg once daily for 5 days and dexlansoprazole MR capsules 30 mg before meals once a day for 5 days were advised. On this visit lidocaine oral topical solution was changed to povidone – iodine germicide Gargle.

Patient said to report reduction in his ulcers after this treatment. Further the patient has been advised for drug sensitivity test for Sulfa drugs.



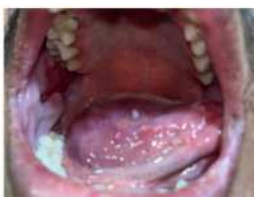


Figure 1. lesion bilaterally involving angle of mouth
Figure 2. Lesion on Tongue

DISCUSSION

Drugs are double edged sword, which gives beneficial results and can also cause adverse reaction in certain conditions. Adverse drug reaction can manifest as many forms like Erythema multiforme, fixed drug eruption and anaphylactic reactions. Erythema multiforme was first reported in literature by Bateman and Bulkey in 1846 followed by Hebra in 1866 who described as erythema exudative multiforme.[4]

Erythema multiforme is an inflammatory skin disorder that is often considered to be a hypersensitivity reaction to certain infections or medications. The condition is believed to involve the immune system's response to triggering factors. EM is a type of hypersensitivity reaction which is caused by various insults, often from an infectious agent or a drug. Antibiotics and NSAIDs may cause erythema multiforme.[6]

A hypersensitive reaction to specific infections or drugs is frequently thought to be the cause of erythema multiforme, an inflammatory skin condition. The immune system's reaction to triggers is thought to play a role in the condition.

Although the precise aetiology of EM is not entirely known, immune complex-mediated hypersensitive response is commonly recognized. This indicates that the EM-specific oral mucosal and skin lesions are caused by immune complexes that the immune system forms in response to specific triggers and deposits in the skin and other tissues.

Cell-mediated immunity appears to be responsible for the destruction of epithelial cells. Early in the disease process, the epidermis becomes infiltrated with CD8 T lymphocytes and macrophages, whereas the dermis displays a slight influx of CD4 lymphocytes. These immunologically active cells are not present in sufficient numbers to be directly responsible for epithelial cell death. Instead, they release diffusible cytokines, which mediate the inflammatory reaction and resultant apoptosis of epithelial cells. In some patients, circulating T cells transiently demonstrate (for < 30 d) a T-helper cell type 1 (TH1) cytokine response (interferon [IFN] gamma, tumor necrosis factor [TNF] alpha, interleukin [IL] 2). Results of immunohistochemical analysis have also shown lesion blister fluid to contain TNF, an important proinflammatory cytokine.[7]

EM minor which typically affects a single mucosa is the most common form and may be associated with symmetrical target lesions on the extremities. EM major is more severe, typically involving 2 or more mucous membranes with more variable skin involvement.[8]

This feature is used to distinguish it from Stevens–Johnson syndrome, where there is extensive skin involvement, significant morbidity, and a mortality rate of 5% to 15%. Although EM is more frequently seen in males, the incidence of drug-related EM is similar in males and females.[5]

EM or EM-like eruption has been only rarely associated with drug intake[8] There is a genetic component of EM. It is linked to specific HLA types such as HLA-DQ3, HLA-B15 (B62), HLA-B35, HLA-A33, HLA-DR53 and HLADQB1*0301. Extensive mucosal involvement may be exceptionally associated with HLA allele DQB1*402 patients.[5]

Recent studies have observed a significant rise in neutrophil count among patients with COVID-19. Neutrophils can release web-like structures called NETs, which capture and immobilize pathogenic microorganisms and produce elevated concentrations of myeloperoxidase (MPO) and defensins to resist exogenous infections.[6]

Currently, there are no cases of these skin eruptions undoubtedly associated with the treatments for COVID-19. Even in patients with such a viral infection and exposed to various drugs, differentiating the cause of EM or EM-like eruptions is difficult.[9]

For example, Reguero et al. reported a 95-year-old female patient who manifested EM lesions 2 days after hospital discharge following SARS-CoV-2 infection and a 10-day cycle of hydroxychloroquine; in this case, the authors did not relate the EM to drugs.[8]

Both EM and EM-like eruptions have been reported as being mainly associated with SARS-CoV-2 infection or, much more rarely, induced by the disease's treatment. These skin eruptions' pathophysiological mechanism could be a hypersensitivity reaction mediated by lymphocytes targeting SARS-CoV-2 antigens in the skin, similar to what was reported for EM associated with other infections. In particular, CD8+ T lymphocytes induce the apoptosis of scattered keratinocytes and lead to satellite cell necrosis.[3]

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