Global Research Journal of Public Health and Epidemiology: ISSN-2360-7920, Vol. 2(3): pp 071-074, May, 2015.

Review

Recurrent erythema multiforme: A dental case report

[1]Jitender Solanki and [2]Sarika Gupta

[1]Associate Professor, Department of Public Health Dentistry, Vyas Dental College and Hospital, India
[2]Postgraduate Student, Oral Medicine and Radiology, Vyas dental college & Hospital

Corresponding Author's E-mail**:** solankijitender@gmail.com

Accepted 27th April

Erythema multiforme is a rare acute mucocutaneous condition caused by a hypersensitivity reaction. It can be triggered with the use of certain drugs or infectious agents, mainly Herpes Simplex virus. It is important to know the etiological factor behind the disease in order to cure the disease or even to prevent attacks in case of recurrent form. This article illustrates a case report of patient with recurrent form of erythema multiforme who responded to antiviral treatment after taking ineffective steroid treatment.

Keywords: Acyclovir, Dapsone, Ulcers, Erythema

INTRODUCTION

Erythema multiforme (EM) is a rare acute mucocutaneous condition caused by a hypersensitivity reaction with the appearance of cytotoxic T lymphocytes in the epithelium that induce apoptosis in keratinocytes, leading to satellite cell necrosis. A number of factors can be associated with EM, but it is found to be mostly associated with preceding infection with herpes simplex virus (HSV). Most other cases are initiated by drugs (Scully and Began, 2008). When recurrent herpes simplex is an important etiologic factor in EM minor, EM major is often preceded with mycoplasmal infections and drug intake. The various etiological factors are given in table 1: (Sokumbi and Wetter, 2012; Rafael Lima Verde Osterne et al., 2009)

Other than these, Nasabzadeh TJ et al in his case report have stated that the precise trigger of a given patient's recurrent EM often remains elusive. He has pointed towards a hormonal influence interpreted as autoimmune progesterone dermatitis (APD), Nasabzadeh et al., 2010.

Care report

An 18 year old male patient came to the OPD with the complaint of ulcers on lower lip since 15 days. Patient was apparently alright uptill 15 days back when he noticed 2 pin point size ulcers on lower lip in the night. Next morning when he got up, the ulcers had markedly increased in size with blood crustations. He gives history of similar ulcers which had developed for the last 2 years in summers, but now they have appeared in winters and are worse. He got relieved with the treatment that he had taken for those ulcers. But this time no relief was achieved. Although ulcers are not associated with pain or burning sensation but were predisposed with an episode of fever for 2 days, patient gives no history of any change in toothpaste or lip cosmetic in the past one month. Patient is under systemic and topical steroids since 5 days but no relief is achieved (tab. Betnisol fort 1 TDSx 5 days, cefadox 500mg 1 BDx 5days, tab. Bfolien plus 1 BDx 7 days, flutibact ointment T/A x7 days). He smokes occassionaly (1-2 cigerettes a day) since 1 year. All his vital signs were within normal limits. Lymph nodes were non tender and non palpable. On inspection lower lip was grossly swollen, cracked, with split crusted bleeding. Widespread fibrin covered erosions were seen with surrounding erythematous area. (Figure 1) Similar lesion was seen on the upper lip but involvement of the lower lip was more. On palpation, the lesion was tender on touch and bleeded profusely. Labial mucosa was Reddish and erythematous. Posteriorly on hard palate a reddish erythematous area was seen which was non tender on palpation ((Figure 2).

Table 1: various etiological factors

Causative agent	Type
Drugs	Antibacterial; anticonvulsants; analgesics; nonsteroidal antiinflammatory drugs; antifungals
Infectious agents	Virus; Herpes simplex, Epstein-Barr virus, Cytomegalovirus, varicella-zoster virus, Mycoplasma pneumonia, hepatitis viruses, Bacterial; Mycobacterium, streptococci, Fungal; parasites

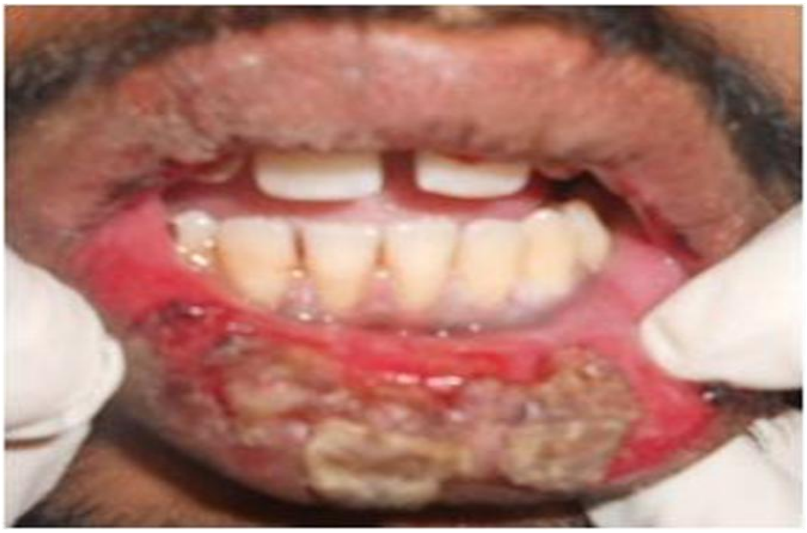

Figure 1: Widespread fibrin covered erosions with surrounding erythematous area seen on lower lip.

Figure 2: Reddish erythematous area seen on hard palate

DISCUSSION

Based upon its clinical spectrum, erythema multiforme has been further grouped into recurrent erythema multiforme and the rare persistent erythema multiforme (Table 2, Drago et al., 1995). According to a study by Schofield JK et al who reviewed the clinical features and treatment of 65 patients with recurrent EM, noted that the mean number of attacks per year was six with the mean duration of 9.5 years, which reflected its chronicity. Maximum patients had oral mucous membrane involvement with mostly viral etiology. Therefore, antiviral drugs, mostly acyclovir was found to be the most effective first-line treatment. Patients who did not

Table 2: Clinical features of various types of EM (3)

CATEGORY OF EM Features	FEATURES
Erythema multiforme minor	Typical target lesions or raised atypical target lesions. < 10% of the body surface area is affected. May affect only the oral mucosa with mild to severe erythema, erosions and ulcers.
Erythema multiforme major	Cutaneous lesions and at least 2 mucosal sites (typically oral mucosa) affected. < 10% of the body surface area involved. Typical target lesions or raised atypical target lesions or both; symmetrically distributed. Severe, widespread oral lesions.
Stevens-Johnson syndrome	Differs from erythema multiforme major in terms of 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. Widespread lesions involving multiple mucosal sites with scarring. Prodromal flu-like systemic symptoms are 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	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 sheets and no macules or target lesions.

respond to acyclovir responded to a small proportion of dapsone. The most resistant patients were treated with azathioprine with complete disease suppression in all cases (Schofield et al., 1993). On the other hand, a study by Tatnall FM et al have shown that continuous acyclovir therapy can completely suppress attacks of recurrent EM and may even lead to disease remission (Tatnall et al., 1993).

The pathophysiology behind herpes simplex virus associated EM (HSV-EM) is cell-mediated immune reaction against viral antigen-positive cells that contain the HSV DNA polymerase gene (pol). It is associated with typical target lesion showing concentric zones of color change (Sokumbi andWetter, 0012).

Histopathologic testing and other laboratory investigations may be used to confirm the diagnosis of EM and to differentiate it from other similar clinical conditions (Sokumbi andWetter, 0012). The pathogenesis of Herpes associated EM includes a virus-triggered autoimmune component (Aurelian et al., 2003).

1. Primary or recurrent HSV infection which may be subclinical or accompanied by visible vesicular lesions.
2. Macrophages and/or $CD34^{+}$ hematopoetic progenitors engulf HSV and DNA is fragmented resulting in generation of DNA fragments that encompass HSV genes including pol.
3. Peripheral extravasation of PBMC carrying HSV DNA fragments possibly related to ICAM-1 expression on endothelial cells
4. Deposition of HSV DNA at distant skin sites
5. Expression of HSV DNA in keratinocytes. The length of HAEM eruption depends upon the duration of gene expression.
6. Infiltration of HSV-specific $CD4^{+}$ Th1 cells in the dermis/epidermis of HAEM lesions Activated T cells have a restricted TCR repertoire and include increased proportion of Vb 2 cells.
7. HSV-specific T cells respond to HSV antigens and generate IFN-g
8. Generation of cytokine and chemokines amplification cascade, including TGF-b, Mig, IP10 and RANTES and recruitment of NK cells, monocytes and leukocytes
9. Recruitment of auto reactive T cells to the lesion site resulting in an autoimmune amplification loop
10. Epidermal cell damage results from attacks by cytotoxic T cells, NK cells and monocytes and/or chermokines in varying combinations
11. TGF-b and $p21^{waf}$ are expressed in keratinocytes at the site and adjacent to the epidermal damage, thereby possibly contributing to apoptotic cell death

Clinically, EM can be confused with urticaria, Stevens-Johnson syndrome, fixed drug eruption, paraneoplastic pemphigus, bullous pemphigoid, Sweet's syndrome, polymorphus light eruption, Rowell's syndrome and cutaneous small-vessel vasculitis. Antiviral prophylaxis is required for patients with HSV-associated recurrent EM and idiopathic recurrent EM. For patients with severe mucosal involvement, hospitalization is considered since it leads to poor oral intake and subsequent fluid and

electrolyte imbalance (Sokumbi andWetter, 0012).

Studies have proven the efficacy of corticosteroids in the treatment of EM but their use as maintenance therapy is not clearly indicated because of the associated side effects. Remission of herpes associated EM can occur by oral acyclovir with short-course which represents a safer, more effective treatment for many patients with recurrent EM. However, EM cannot be prevented if administered after a herpes simplex recurrence has occurred. Repeated topical treatment with acyclovir to sites of recurrent herpes infection is said to prevent erythema multiforme. It has been seen in several studies that acyclovir completely suppress recurrent EM in the majority of patients and produce partial suppression in others (Huff et al., 1983).

Continuous acyclovir therapy in patients who have a clear-cut relationship between HSV and EM are often effectively treated with acyclovir (200 mg 5x/day for 5 days) started at the earliest sign of a herpes attack. But patients who have frequent attacks of EM, whether HSV-related or not, should receive a trial of continuous acyclovir before alternative therapies are tried. It is not clear whether failures of acyclovir are related to viral resistance to acyclovir or to non-HSV-induced recurrent EM. One case report discussed a patient with frequent post-herpetic recurrent EM resistant to continuous acyclovir treatment but responsive to valacyclovir (Huff et al., 1983). The use of thalidomide should be reserved for severe cases(Leaute-Labreze et al., 2000). The efficacy of dapsone in treating recurrent EM has been reported earlier. Antimalarials (mepacrine or hydroxychloroquine) have also resulted in disease suppression where acyclovir treatment has failed. But it is recommended as a second line treatment due to the associated side effects. Mycophenolate mofetil has been shown to be an effective and relatively safe immunosuppressive agent in recurrent EM in case of failure to anti malaria's. However, its high cost limits its use (Sen and Chua, 2004).

CONCLUSION

The most important step in the management of erythema multiforme or similar cutaneous lesions is proper history taking. This is done to rule out the correct etiology of the disease. Treatment is aimed based upon the causative factors like virus or drug related. The use of corticosteroids is most prevalent in case of erythema multiforme. However, many side effects have been reported with its use for a longer duration. In the present case report when the patient could not be cured with steroids a treatment plan consisting of antiviral drug helped. Therefore, it is important to rule out the etiology before forming a proper treatment plan.

REFERENCES

Scully C, Began J (2008). Oral mucosal diseases: Erythema multiforme. British Journal of Oral and Maxillofacial Surgery;46(2):90–95.

Sokumbi O, Wetter DA (20012). Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int. J. Dermatol.; 51(8):889–902.

Rafael Lima Verde Osterne et al (2009). Management of Erythema Multiforme Associated with Recurrent Herpes Infection: A Case Report. JCDA.;79:597-601.

Nasabzadeh TJ, Stefanato CM, Doole JE, Radfar A, Bhawan J, Venna S (2010). Recurrent erythema multiforme triggered by progesterone sensitivity. J. Cutaneous Pathol.;37(11):1164–1167.

Drago F, Parodi A, Rebora A (1995). Persistent erythema multiforme: Report of two new cases and review of literature.;33(2):366-369.

Schofield JK, Tatnall FM, Leigh IM (1993). Recurrent erythema multiforme: clinical features and treatment in a large series of patients. Brit. J. Dermatol.;128(5):542–545.

Tatnall FM, Schofield JK, Leigh IM (1993). A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. Brit. J. Dermatol.;132(2):267–270.

Aurelian L, Ono F, Burnett J (2003). Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): A viral disease with an autoimmune component. Dermatology Online J.; 9(1):1-12.

Huff JC, Weston WL, Tonnesen MG (1983). Erythema multiforme: A critical review of characteristics, diagnostic criteria, and causes. J. Am. Acad. Dermatol.;8(6):763–775.

Leaute-Labreze C, Lamireau T, Chawki D, Maleville J, Taieb A (2000). Diagnosis, classification, and management of erythema multiforme and Stevens–Johnson syndrome. Arch Dis Child;83:347–352.

Sen P, Chua SH (2004). A Case of Recurrent Erythema Multiforme and its Therapeutic Complications. Ann Acad Med Singapore.