Scholars Academic Journal of Biosciences (SAJB) **ISSN 2321-6883 (Online)**
Sch. Acad. J. Biosci., 2015; 3(8):640-643 **ISSN 2347-9515 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Case Report

Management of Non Healing Oral Ulcer in Diabetic Patient Using Topical Application of Epidermal Growth Factor: A Case Report

Dr. Richik Tripathi*[1], Dr. Kamlakar Tripathi[2]
[1]Service Senior Resident, Oral Maxillofacial Surgery Divison, Faculty of Dental Sciences, Institute of Medical Science, Banaras Hindu university, Varanasi, India
[2]Institute of Medical Science, Banaras Hindu University, Varanasi, India

***Corresponding author**
Dr. Richik Tripathi
Email: richik.tripathi@gmail.com

Abstract: Epidermal growth factor (EGF) is used widely in management of diabetic foot wounds to augment wound healing and to promote epithelialization. There are reports of its use in management of oral mucositis in patients receiving head and neck radio therapy. However reports of its use in management of diabetic oral ulcers are rare. we present here a case of non healing diabetic oral ulcer which we managed using topical EGF. A 45 year old patient who is suffering from diabetes presented with non healing ulcer of oral cavity. Based on reports of investigations the ulcer was diagnosed as non healing major aphthous ulcer. Oral hypoglycemic and insulin therapy was started to manage hyperglycemia. Normal glycemic control was achieved in 5 days and topical EGF and antiseptics were given to augment ulcer healing. Healing started on 8th day and progressed to complete healing by 21st day. Topical epidermal growth factor can be used effectively in management of non healing diabetic ulcers of oral cavity.
Keywords: Epidermal growth factor (EGF), diabetic foot, radio therapy.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiology characterised by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism. It is one of the leading causes of death worldwide [1]. Unlike other organs, oral cavity is greatly affected by diabetes. Significant changes are observed in oral microflora, salivary glands and periodontium in oral cavity while immune system of body is compromised during hyperglycemic episodes in diabetics [1]. Nearly all the vital organs/organ system in body are severely affected by diabetes. Aphthous ulcers which is common in 2 or 3rd decade of life responds readily to topical antiseptics and heals within one week [2] but in diabetics healing process is disturbed and ulcers persist for longer period [3]. A number of factors are responsible for non healing or delayed healing of oral ulcers in diabetics, one of which is reduced secretion of epidermal growth factor in saliva and reduced flow rate of saliva [4,5]. Epidermal growth factor is used widely in management of diabetic foot ulcer to augment wound healing. There are reports of its use in management of oral mucositis in patients receiving head and neck radiotherapy [6]. However reports of its use in oral cavity for management of non healing oral ulcers are rare. We present here a case of non healing ulcer in oral cavity which we managed using topical EGF.

CASE REPORT

A 45 year old patient reported to the outpatient department (OPD) of oral and maxillofacial surgery with a chief complaint of non healing ulcer on palate since 6 months. Patient was asymptomatic 6months back when he developed small minute ulcer on palate, which later progressed in size. He consulted a local dentist who prescribed him local antiseptics and oral anti inflammatory. Upon taking medications his pain was relieved but ulcer persisted. He took further consultation from otolaryngologist who advised him blood sugar testing and prescribed local corticosteroids and oral rebamipide which he took for one week. Unrelieved of his complaints patient finally presented to oral and maxillofacial surgery OPD. Upon examination patient was well oriented to time place and person. He had medical history of diabetes since 5 years and he was regularly taking oral hypoglycemic agent. Patient was non smoker and non tobacco chewer. He was working in state government sponsored public welfare programme. He admitted that he often feel stressed due to excessive work load. Extra oral lymph nodes were not palpable. Intra-orally rounded ulcer of 8mm diameter (figure-1) was present on left side of palate. No other abnormality or pathology was detected in oral cavity. Edges of ulcer were erythematous and bed of ulcer was filled with granulation tissue. Ulcer was very painful to touch. We provisionally diagnosed it as chronic non healing aphthous ulcer. Patient was

advised for complete blood count, blood sugar test and digital panoramic x-ray to rule out any dental abnormality. His fasting blood sugar level was 156 mg/dl, post prandial (PP) level was 210 mg/dl and HbA1c level was 7.6. Complete blood count test was within normal limits and no dental or bony abnormality was detected on panoramic x-ray. To rule out other causes collagen profiling, iron and Vit B12 level test and peripheral blood picture was advised. All test results were within normal limits. Brush biopsy revealed absence of metastatic cells and presence of chronic inflammatory cells. Based on these finding we finally diagnosed this lesion as chronic non healing major aphthous ulcer.

TREATMENT

Patient was informed about treatment procedure and beneficial / harmful effects of epithelial growth factor. Written consent was obtained from patient as per Helsinki declaration. After consultation with senior surgeons and pharmacologist treatment was started. Initially patient was referred to an experienced diabetologist to control blood sugar level. Diabetologist modified his drug therapy to Repaglinide 1 mg plus Metformin 500 mg once daily and 20 units of pre-mixed insulin analogue (30/70). Diet restrictions and moderate exercise was also advised. Ointment containing epithelial growth factor 60mcg and another ointment containing combination of Metronidazole 1% w/w and Chlorhexidine 0.25% w/w 1gm was started. Oral antioxidants plus lycopene and prednisolone 20 mg twice daily was also started. Within 5 days his PP and Fasting level was 128 and 95 respectively, but there were no signs of ulcer healing . On the 8th day epithelialization at the margins of ulcer was seen which progressed to half the area of ulcer by 14th day(figure-2). Epidermal growth factor application was discontinued from 14th day and oral prednisolone dose was tapered to 10mg twice daily while metronidazole and chlorhexidine ointment was continued. By the 21st day there was complete epithelialization of the ulcer (figure-3).

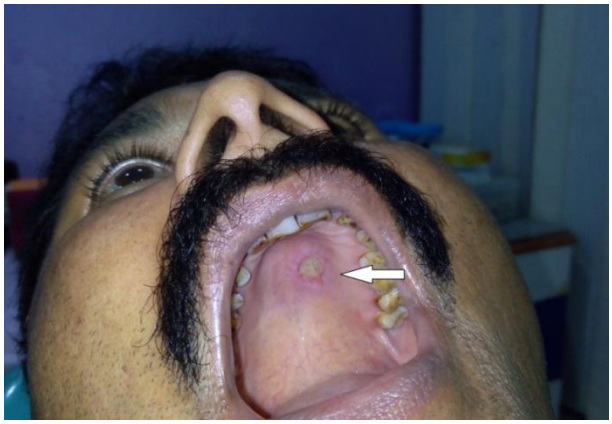

Fig-1: Ulcer on the anterior palate at the time of presentation

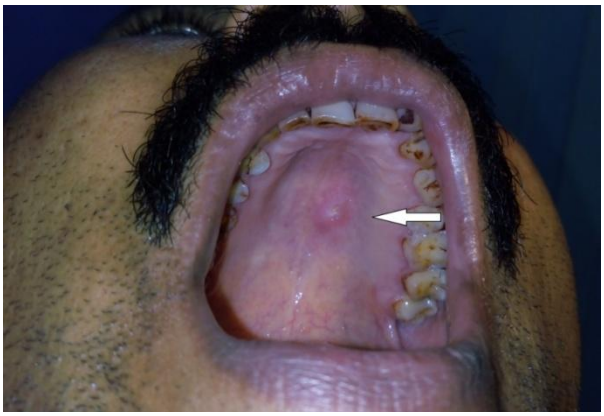

Fig-2 : Ulcer on the 14th day of therapy

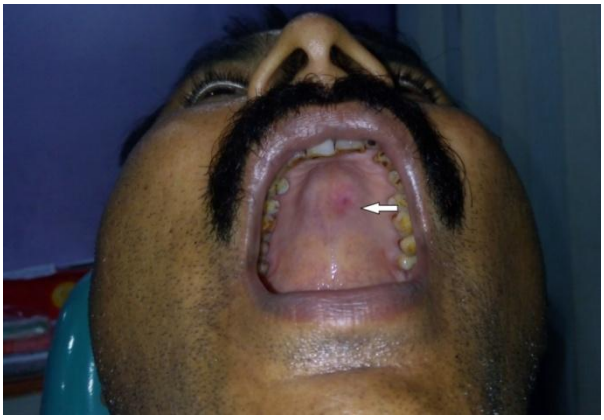

Fig-3: Complete healing by 21st day

DISCUSSION

Aphthous ulcer is very common in second and third decade of life. Its etiology remains unclear [2] but evidences suggest various factors are responsible for its occurrence. These are Genetic factors, trauma, stress, Gastrointestinal disorder, Vitamin deficiency, Autoimmune disorders, Infection and fluctuations in level of certain hormones [2]. Systemic disorders are modifying factors for oral ulcers. Diabetes is one of the most common disorder of modern civilization and it is very important modifying factor responsible for persistent non healing oral ulcers. Diabetes is associated with vascular sclerosis, leading to poor tissue perfusion which causes hypoxia and impaired wound healing [1]. Hypoxia enhances initial inflammatory reactions and increases oxidant free radical, which delays wound healing.

Diabetic patients are under state of immunosuppression. Accumulation of advanced glycosylation end products (AGE) causes decrease in number of migrated neutrophils at the site of inflammation. AGE are known to directly alter the neutrophil function including chemotaxis. Salivary gland in diabetics becomes hypofunctional due to accumulation of AGE and poor autonomic innervation. Flow rate of saliva is significantly reduced in diabetics [3,4]. Saliva contains many kinds of antimicrobial peptides and proteins and the lower flow rate causes

bacterial infection due to poor cleansing action of saliva. The components of saliva are altered in diabetics. Saliva in diabetics contains less glutathione and melatonin that function as a scavenger for free radicals than that in healthy individuals [4]. Diabetic patients produce more free radicals at the wound under elevated blood-sugar and hypo oxidation conditions than under normal condition [4,5].

Epidermal Growth Factor

Epidermal growth factor is a small protein (53 amino acids) which has been found to enhance epidermal growth and keratinisation [7,8]. EGF directly stimulates the proliferation of epidermal cells, and this stimulatory action of EGF is independent of other systemic or hormonal factors [7]. It plays significant role in maintaining oral health, promoting wound healing, and maintaining mucosal integrity [8]. It was first identified in mouse salivary gland later it was found to be present in human salivary glands. Dr Stanley Cohen [8] did extensive study on EGF. He identified and isolated it from mouse saliva and studied its role on cell proliferation and differentiation. Margaret Niall *et al*. [9] did comparative study on wound healing of sialectomized and non sialectomized mouse. He concluded that in sialectomized mouse wounds heals much slower compared to non sialectomized mouse and EGF is an important constituent of saliva which augments wound healing. Works of Gregory L. Brown [10] on human skin wounds proved that EGF plays important role in early healing of skin wounds. During the period of 1999 to 2006 [10-13] EGF containing ointments became the gold standard to promote early healing of diabetic wounds. Oxford GE *et al.* [15] evaluated 21 diabetic patients to determine concentration of EGF in saliva. They found that diabetic people have significantly reduced epidermal growth factor level in saliva compared to non diabetics. Reduction in salivary EGF not only increases risk of periodontal diseases but also impairs wound healing. Nagy A *et al.* [16] showed improved oral ulcer healing in diabetic mouse when EGF supplement was provided in drinking water. Providing external growth factor not only restores EGF to required level but also augments wound healing. EGF is mitogenic both for normal and neoplastic cells[17,18] but its sole action as promoter of carcinogenesis has not been proven. In oral cavity use of EGF as therapeutic agent to promote oral wound healing is limited. There have been very few studies regarding use of epithelial growth factor in management of non healing wounds in oral cavity. In our case we used it with caution and discontinued its application once epithelialization started. Result was excellent and we recommend further studies enrolling higher number of diabetic patients in study.

CONCLUSION

Topical epidermal growth factor can be used effectively in management of non healing diabetic ulcers of oral cavity.

REFERENCES

1. Al-Maskari AY, Al-Maskari MY, Al-Sudairy S; Oral manifestations and complications of diabetes mellitus: a review. Sultan Qaboos University Medical Journal, 2011; 11(2):179.
2. Preeti L, Magesh KT, Rajkumar K, Karthik R; Recurrent aphthous stomatitis. Journal of oral and maxillofacial pathology: JOMFP, 2011; 15(3): 252.
3. Gümüs P, Buduneli N, Cetinkalp S, Hawkins SI, Renaud D, Kinane DF, Scott DA; Salivary antioxidants in patients with type 1 or 2 diabetes and inflammatory periodontal disease: a case-control study. Journal of periodontology, 2009; 80(9): 1440-1446.
4. Cutando A, Gómez-Moreno G, Villalba J, Ferrera MJ, Escames G, Acuña-Castroviejo D; Relationship between salivary melatonin levels and periodontal status in diabetic patients. Journal of pineal research, 2003; 35(4): 239-244.
5. Costa PP, Trevisan GL, Macedo GO, Palioto DB, Souza SL, Grisi MF, Taba Jr, M; Salivary interleukin-6, matrix metalloproteinase-8, and osteoprotegerin in patients with periodontitis and diabetes. Journal of periodontology, 2010; 81(3): 384-391.
6. Wu HG, Song SY, Kim YS, Oh YT, Lee C. G, Keum KC, Lee SW; Therapeutic effect of recombinant human epidermal growth factor (rhEGF) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer,Cancer. 2009; 115(16): 3699-3708.
7. Jorissen R N, Walker F, Pouliot N, Garrett TP, Ward CW, Burgess AW; Epidermal growth factor receptor: mechanisms of activation and signalling. Experimental cell research, 2003; *284*(1): 31-53.
8. Carpenter G, Cohen S; Epidermal growth factor. Annual review of biochemistry, 1979; *48*(1): 193-216.
9. Niall M, Ryan GB, O'Brien BM; The effect of epidermal growth factor on wound healing in mice. Journal of Surgical Research, 1982; *33*(2): 164-169.
10. Brown G L, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtsinger III LJ, Lynch JB; Enhancement of wound healing by topical treatment with epidermal growth factor. New England Journal of Medicine, 1989; *321*(2): 76-79.
11. Steed DL; The role of growth factors in wound healing. Surgical Clinics of North America, 1997; *77*(3): 575-586.
12. Feng J, Du, WH, Wang J; Clinical study of various growth factors on the improvement of impaired

healing ulcers in patients with diabetic disease. Zhongguo xiu fu chong jian wai ke za zhi= Zhongguo xiufu chongjian waike zazhi= Chinese journal of reparative and reconstructive surgery,1999; 13(5): 273-277.

13. Hong JP, Jung HD, Kim YW. Recombinant human epidermal growth factor (EGF) to enhance healing for diabetic foot ulcers. Annals of plastic surgery, 2006; 56(4): 394-398.
14. Acosta JB, Savigne W, Valdez C, Franco N, Alba JS, Rio AD, Férnandez-Montequín J; Epidermal growth factor intralesional infiltrations can prevent amputation in patients with advanced diabetic foot wounds. International wound journal, 2006; 3(3): 232-239.
15. Oxford GE, Tayari L, Barfoot MD, Peck AB, Tanaka Y, Humphreys-Beher MG; Salivary EGF levels reduced in diabetic patients. Journal of diabetes and its complications, 2000; *14*(3): 140-145.
16. Nagy A, Nagashima H, Cha S, Oxford GE, Zelles T, Peck AB, Humphreys-Beher MG; Reduced oral wound healing in the NOD mouse model for type 1 autoimmune diabetes and its reversal by epidermal growth factor supplementation. Diabetes, 2001; 50(9): 2100-2104.
17. Stoscheck CM, King LE; Role of epidermal growth factor in carcinogenesis. Cancer research, 1986; *46*(3): 1030-1037.
18. Crew AJ, Langdon SP, Miller EP, Miller WR; Mitogenic effects of epidermal growth factor and transforming growth factor-α on EGF-receptor positive human ovarian carcinoma cell lines. European Journal of Cancer, 1992; 28(2): 337-341.