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Nicorandil Induced Oral Ulceration - A Case Report and Review of Literature

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Abstract:

Nicorandil, an antianginal drug is being commonly used worldwide (except in United States) across the spectrum of the coronary artery disease. It has been recognised as a causative factor for oral ulceration. The aim of this case report is to increase awareness among the cardiologists that nicorandil can induce persistent oral ulceration and thereby look for the same during the follow up in the patients who are prescribed nicorandil.

Keyword *- Nicorandil Coronary Artery Disease Oral ulceration Hypersensitivity*

1. Introduction

Coronary artery disease (CAD) is the most common cause of mortality worldwide. Patients are at increased risk of having recurrent angina after a manifested CAD. Angina prevention is an important factor during rehabilitation of patients with manifested CAD. Nitrates have been the most common antianginal drugs, but have a risk of intolerance on long term usage. Nicorandil, a novel drug, has both venodilation and arteriolar dilation like the nitrates with no intolerance. Oral ulceration is an important adverse effect to be kept in mind while monitoring patients who are on nicorandil.[1]

We report a case of oral ulceration secondary to use of nicorandil and review the literature regarding the association.

2. Case

A 49 year male was referred to a dentist by his general practitioner for evaluation of painful ulcer over the tongue. The patient reported to have ulceration over the tongue for the past one month.There was no previous history of oral ulceration. He had no comorbidities. He had undergone coronary artery bypass surgery (CABG) 6 months back. His medications included nicorandil 5 mg twice daily, aspirin, clopidogrel, atorvastatin, carvedilol, ramipril, torsemide and ranitidine. He had been prescribed triamnicolone acetonide 0.1% paste and Chlorhexidine mouthwash for his oral ulceration and was advised to avoid spicy foods.

On examination, there was a single oval ulcer measuring 15 mm in diameter on the lateral border of the tongue with punched out appearance. The ulcer floor has a yellowish pseudomembrane. The ulcer was painful but not indurated. Irritation by the teeth was not evident. (Figure 1).There was no erythematous flare surrounding the ulcer. The remaining oral mucosa was normal. There was no lymph nodal enlargement. There was no cutaneous, ocular or genital lesions. A biopsy was ordered as there was no response to the initial treatment prescribed for ulcer. The tissue was sent for histopathological and direct immunofluorescence to rule out the possibility of oral carcinoma. The histopathology reported eosinophilic infiltration and non specific ulceration. The direct immunofluorescence was negative. The patient was prescribed Betamethasone 0.05% mouthwashes and the physician was informed of the likely association of nicorandil and the ulceration.The patient has been referred to our department regarding the discontinuation the nicorandil. After discontinuing nicorandil, the ulcer subsided over 2 weeks (Figure 2).

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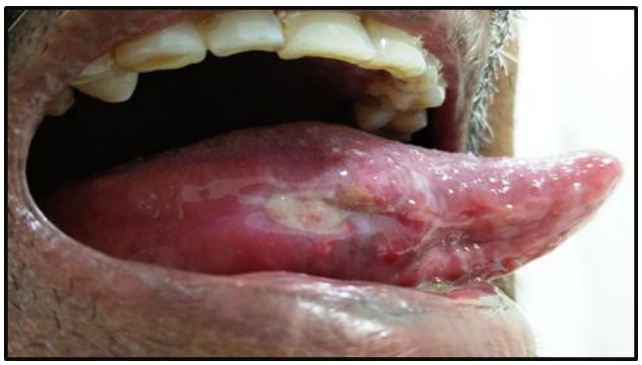

Figure 1: large painful ulcer measuring 15 mm on left lateral border of tongue, demonstrating the punched out appearance. The floor of the ulcer is having yellowish pseduomembrane.

Figure 2: After discontinuation of nicorandil, the lateral border mucosa became normal and ulcer subsided with no scar.

3. Discussion

Nicorandil, a novel antianginal drug for the treatment and prevention of angina was first developed in Japan in 1980s and has been in Europe since last decade.[1] It is both a nicotinamide ester and a potassium channel activator. The usage of nicorandil has been on rise in patients across the spectrum of coronary artery disease due to its efficacy and absence of tolerance as seen with nitrates. It is indeed can be called as an hybrid drug with nitrate like action causing venodilation and potassium channel activation causing arteriolar dilation. It reduces both preload and afterload.[2]

The common adverse effects of nicorandil is headache, which is evident in one third of the patients during the initial days of treatment.[3] Other less frequent adverse events are flushing, nausea, dizziness, hypotension and tachycardia.[3] Oral ulceration has been recognized as an adverse effect but the awareness of it among cardiologists is less as most of the reports were published in French and European Literature with none in other parts of the world.[4,5,6,7,8]

The first case report of oral ulceration in association with use of nicorandil was in 1997s[4] and subsequently approximately around 53 case reports have been published to the best of our knowledge in oral dentistry journals and one in the cardiology British Heart Journal.[9] It is an attempt to increase awareness among the treating cardiologists and physicians regarding the distressing adverse effect on the usage of nicorandil, as the use of this drug is on uprise and recently in treatment of hypertension.

The prevalence of nicorandil induced ulceration is around 5% as evaluated prospectively in 100 patients by Marquart - Elbaz et al.[10] Other sites of mucosal ulceration were reported in the gastrointestinal tract,[11] anal (Watson et al)[12] or perianal region,[13] penis,[14] and vulvo or vulvovaginal[15] region. The prevalence of ulceration among these sites is not known but the nicorandil seems to induce ulceration mostly at mucocutaneous interface zones of the body.[16]

The mechanism of ulceration is clearly not known and several hypothesis have been formulated secondary to the use of nicorandil, they are 1) A direct local effect of the electrolyte imbalance induced by nicorandil in the oral mucosa.[17] 2)An hypersensitivity reaction to nicorandil[9] 3) A disturbance similar to vascular steal phenomenon caused by redistribution of arterial and venous flow making the mucosa susceptible to ulceration[18] 4) An inhibitory effect of type 1 plasminogen activator inhibitor activity which reduces anti-inflammatory action.[19] The predominant involvement of oral mucosa and tongue suggests the role of involvement of local/anatomic physiological factors for the development of ulcer.

A dosage more than 30 mg/d leads to ulceration[20] but dosage as low as 10 mg/day can cause ulceration as seen in our patient. Dosage modification in patients who are using high doses or stoppage of drug is needed.[9]

In conclusion, the drug nicorandil is being used commonly for prevention of angina and for treating hypertension. It can have a very distressing complication of causing oral ulceration at any dosage and should be kept in differential diagnosis when considering an ulceration in the patients being treated over the mucocutaneous surfaces. A dosage reduction in the patients who are on high doses and stoppage of the drug with low doses is needed to overcome the issue as it is usually no respondent to treatment.

4. Conflicts of Interest

No conflicts of interest by the authors.

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