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Oral ulcers caused by hydroxyurea

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Abstract
We present a case of oral ulceration in a patient with essential thrombocythaemia, that proved to be secondary to treatment with hydroxyurea. This complication has not yet been reported in the ENT literature. Hydroxyurea should be considered as a possible cause of persistent oral ulceration in patients with haematological conditions. It should be noted that the onset of this complication is not related to the dose and duration of therapy.

Key words: Hydroxyurea, Adverse Effects; Oral Ulcer; Stomatitis

Case report

A 68-year-old male presented with a two-month-old complaint of sore mouth. He had been treated earlier with mouthwashes and steroid pellets with no response. His past medical history was remarkable in that he had been diagnosed to have essential thrombocythaemia eight years ago when he presented with fatigue and a blood count revealed thrombocytosis of 1229×10^9/l and a haemoglobin of 7.2 grams per cent. His weight at the time of presentation was 90 kg. He was initially started on daraprim but this was subsequently changed to hydroxyurea. The dose of hydroxyurea was raised to 0.5–1 gm per day over the years. He was also on allupurinol to control his gout. He needed regular transfusions for the anaemia caused by hydroxyurea. The dose of hydroxyurea had been gradually increased to 2 g per day five months prior to presentation, when he weighed 110 kg. The patient had no other medical problems.

Clinical examination revealed gingivitis and erythema of the palate. There were diffuse erosive changes in the buccal mucosa and the tongue. Ear, nose and throat examination was otherwise unremarkable. Blood counts were normal. He was initially placed on fluconazole for suspected candidiaisis and metronidazole to combat anaerobes. A mouth swab, however, grew normal upper respiratory flora. His symptoms worsened with the above treatment after two weeks. Biopsy of the buccal mucosa was undertaken to rule out bullous diseases and lichen planus. This revealed only non-specific inflammation.

A subsequent literature review identified hydroxyurea to be a probable cause of mouth ulcers. The mouth ulcers completely subsided within two weeks when hydroxyurea was stopped. He is currently on busulphan.

Discussion

Mucositis is a common side-effect of anti-cancer chemotherapy and oral problems occur in 40 per cent of patients receiving chemotherapy. Patients with haematological problems are two to three times more likely to develop oral problems following chemotherapy compared to those with solid tumours.[1] Mucositis typically affects the non-keratinized epithelium in the oral cavity such as the cheek, soft palate, ventral surface of the tongue and the floor of the mouth. Onset is usually five to seven days after drug administration, a few days before the haematological nadir. Notable drugs causing stomatitis include 5-fluorouracil, methotrexate, doxorubicin, daunorubicin, bleomycin and ara-C. Stomatitis caused by these drugs is influenced by the dose and schedule of the drugs, combination therapy and the state of renal and hepatic function. Oral cooling helps reduce the severity of 5-fluorouracil induced stomatitis. Local application of cytokines, such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor has been shown to be effective and optimal use is being investigated.[2]

Hydroxyurea is an anti-neoplastic agent with a low toxicity profile used to treat myeloproliferative disorders and other non-neoplastic conditions including human immunodeficiency virus (HIV) disease. Several mechanisms of action have been described, including inactivation of the enzyme ribonuclease reductase with subsequent inhibition of cellular DNA synthesis and cell death.

It is well known to cause cutaneous side-effects such as diffuse hyperpigmentation, brown discoloration of nails, photosensitization, acral erythema, fixed drug eruption and alopecia.[3] A poikilodermatous dermatomyositis-like skin eruption has also been documented.[4] Leg ulcers, typically occurring over the malleoli, are seen with long-term therapy.[5,6] This is secondary to cutaneous atrophy and poor wound healing. Histological findings in leg ulcers are non-specific. A recent study of 14 patients with leg ulceration revealed that cessation of therapy was essential for healing or improvement.[7]

Owing to the high rate of cellular turnover in the oral mucosa, the basal cells are susceptible to damage. With long-term therapy, accumulation of cellular injury overwhelms repair mechanisms leading to tissue damage and ulceration. Brinckner *et al.*[8] described acute mucocutaneous side-effects when high doses of the drug (10 g per day) were administered. Norhaya *et al.*[9] have described five patients with painful oral ulcers following hydroxyurea

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therapy for haematological problems. The dosage in the latter series for all patients was between one and 2.5 g per day. The symptoms resolved when the drug was withdrawn and reappeared in one patient when the drug was re-introduced. Richard *et al*.[10] described erosive stomatitis as part of a chronic dermatomyositis-like picture following hydroxyurea therapy.

It is of note that as in leg ulcers[5] there appears to be no consistent correlation between the dose and duration of hydroxyurea therapy and the appearance of oral ulcers. This lack of correlation may lead to the drug not being considered as the cause of stomatitis, especially in patients who have been on the drug for a while. The duration of therapy prior to onset of stomatitis ranges between one month and four years.[9,10]

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