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CLINICAL RECORD

Ulceration of the nasal dorsum: a rare cause?

F SALIM, A JOSHI, C HOPKINS

ENT Department, Guy's Hospital, London, UK

Abstract

Introduction: Non-healing ulcers can be caused by a number of conditions, including vascular disease, diabetes, malignancy and some infections. Drug-related ulcers are rare, and a high index of clinical suspicion is required for diagnosis, in parallel with exclusion of more sinister underlying causes.

Case report: We present a patient with a complex medical background, who had a 10-week history of a non-healing ulcer on his nasal bridge. Inflammatory, autoimmune and malignant causes for the ulcer were excluded by histopathology.

Conclusion: Nicorandil was deemed to be the most likely cause for the patient's ulcer. Nicorandil is an anti-anginal medication known to cause oral ulceration and skin lesions in the perianal and peristomal regions and around surgical wounds. However, there are no previously reported cases of facial ulcers. The ulcer required surgical debridement and healed completely within six months, following discontinuation of nicorandil. This case highlights the importance of having a high index of clinical suspicion regarding non-healing ulcers, and of considering drugs as an aetiological factor, especially in patients with a complex medical background who are taking numerous medications.

Key words: Nicorandil; Ulcer; Mucous Membrane Pemphigoid, Benign; Adverse Effects

Introduction

Non-healing ulcers are defined as ulcers that fail to heal within three to four weeks. Tender facial ulcers are very distressing for patients physically and psychologically. Prompt diagnosis is therefore of major importance in these patients. Common aetiological factors include vasculitis, diabetes mellitus, trauma, cutaneous malignancy and infections. A comprehensive medical history and extensive investigations are usually required to reach a final diagnosis.

In cases where investigations yield no outcome, rare causes of skin ulceration such as therapeutic medication should be suspected. Elderly patients with multiple medical issues who take more than 5 types of medications have been reported to have an increased risk of developing adverse drug reactions, of up to 3 per cent.[1] The majority of patients with adverse drug reactions present with simple rashes; however, a small number can present with very debilitating or life-threatening symptoms.

We report the case of a 64-year-old man with a complex medical background who was referred to the ear, nose and throat clinic with a 10-week history of a painful, non-healing ulcer on the dorsum of his nose.

Case report

A 64-year-old man presented with a history of blisters in the floor of his mouth and gingivae, and was diagnosed with mild mucous membrane pemphigoid. Mucous membrane pemphigoid was confirmed histopathologically after taking a biopsy from the gingivae, which was positive for linear immunoglobulin (Ig) G, IgA and complement.[2]

The patient's medical history was significant for ischaemic heart disease, hypertension, chronic obstructive pulmonary disease, dysphagia, and unexplained, significant weight loss. Barium swallow, oesophagoscopy and colonoscopy did not reveal any significant findings to explain his symptoms. He had been prescribed multiple medications to improve his symptoms. He was subsequently diagnosed with obstructive sleep apnoea and commenced on continuous positive airway pressure ventilation, using a full face-mask, by the respiratory physicians.

He re-presented with a tender ulcer on the dorsum of his nose, which was initially attributed to pressure secondary to prolonged use of the continuous positive airway pressure mask. The ulcer failed to heal despite discontinued use of the continuous positive airway pressure mask.

The patient therefore underwent an initial biopsy, histological analysis of which revealed a non-specific ulcer, with repeated biopsies yielding similar results. Neither topical nor oral medications, including systemic steroids, led to any improvement in the ulcer.

The patient developed severe pain over the dorsum, at which point he was referred to the ENT department, approximately 10 weeks after initial presentation of his ulcer. Examination revealed an ulcer that was approximately 0.7 by 1.2 cm with a deep, non-granulating base exposing the underlying nasal bones, and with well defined, 'punched out' edges (Figure 1). Another biopsy was performed, and histological analysis was reported as showing a fibroepithelial ulcer with no evidence of neoplasia.

Careful review of the patient's medical history revealed that he had been taking nicorandil 20 mg a day for the past

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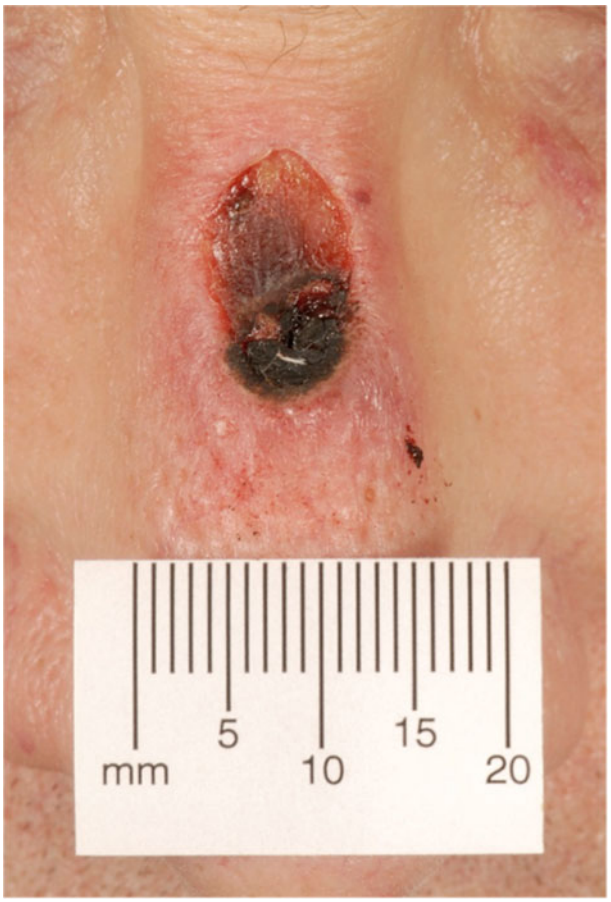

FIG. 1
Clinical photograph showing the ulcer at first presentation.

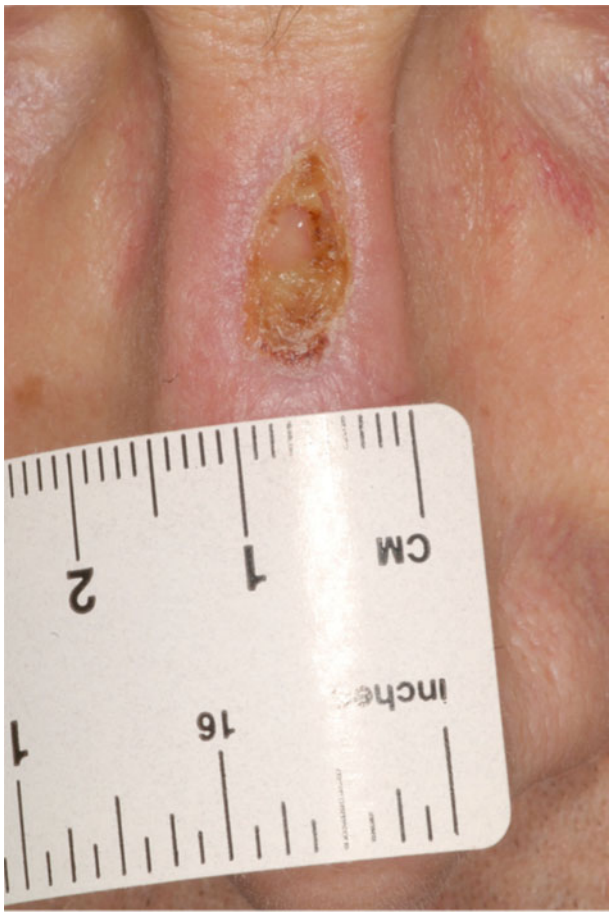

FIG. 2
Clinical photograph showing the ulcer one month after cessation of nicorandil.

3 years for his ischaemic heart disease. We suspected that his ulcer, dysphagia and weight loss could be side effects of the drug. Nicorandil was cautiously discontinued following consultation with the patient's cardiologist. The ulcer started to show signs of healing (Figure 2) within a month of stopping nicorandil. Primary closure was undertaken a month later as the bone over the dorsum remained exposed. The ulcer had healed completely at four months (Figure 3), with significant improvement in the patient's nasal tenderness. Twelve months after presentation, he remained well with improvement in his dysphagia and weight loss.

Discussion

Nicorandil is a commonly used anti-anginal drug which acts by activating adenosine triphosphate sensitive potassium channels and a nitric oxide donor, resulting in decreased cardiac preload and afterload.[3] Nicorandil-related oral ulcers were first reported around 1997.[4] This was followed by reports of nicorandil-associated ulcers beyond the oral mucosa involving the perianal, vulval and peristomal regions, as well as around surgical wounds.[5] Other recognised side effects associated with nicorandil include headaches, nausea, cutaneous erythema, weight loss and dysphagia.[6]

Nicorandil-associated ulcer formation has been reported to be dose-related, with most cases related to an increase in dose.[5,7] The threshold dose for development of ulcers has been reported to be between 20 and 80 mg. Our patient was on a 20 mg daily dose for approximately 36 months. Previous reports have described ulcers developing as early as 4 weeks after commencing medication, although the timeframe reported ranges from 4 weeks to 36 months.[8]

A possible mechanism of action of nicorandil is inhibition of leukocyte activation and migration, thereby causing a reduction in microvascular obstruction in ischaemic cardiac tissue.[3,9] However, this inhibition of leukocyte migration and activation may also cause delayed early wound healing. Less convincing proposed theories include (1) a vas-

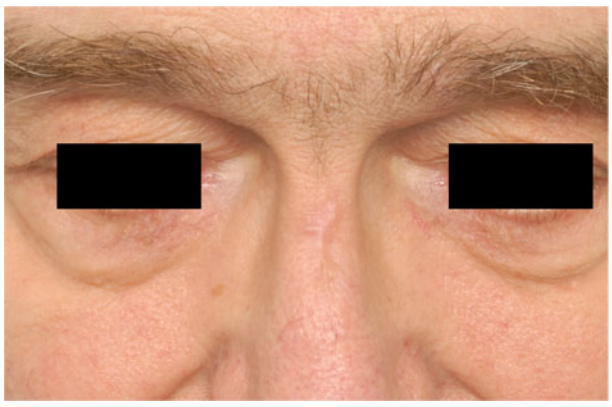

FIG. 3
Clinical photograph at four months, showing complete healing of the wound.

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cular steal phenomenon and (2) excretion of a toxic metabolite of nicorandil into the gut.[5] Early studies on rats suggested that nicorandil may have a similar gastroprotective effect to cimetidine in experimentally induced gastric ulcers,[10] hence making it an unusual ulcer-causing drug.

Nicorandil ulcers usually present as tender lesions extending quite deeply, with minimal granulation tissue in their base and very well defined edges. A literature review by Boulingez and Bonnetblanc on nicorandil-induced oral ulcers showed a 5 per cent incidence rate with lesions varying in size from 0.5 to 3 cm. Ulcers usually start to heal and pain levels drop within 1 to 12 weeks of discontinuing the medication.[11] The decision to stop nicorandil should only be made after consultation with the patient's cardiologist.

In our patient's case, the known history of mucous membrane pemphigoid delayed the final diagnosis of nicorandil-induced ulceration. Mucous membrane pemphigoid is a rare, autoimmune, subepidermal, bullous disease characterised by erosive lesions on the mucous membranes and skin. Diagnosis is via direct immunofluorescence, which will reveal linear deposition of IgG, complement 3 or, less commonly, IgA along the basement membrane zone. Mucous membrane pemphigoid has been reported to affect skin despite it being a disease mainly of mucous membranes.[12]

- **Nicorandil ulcers commonly cause oral, peristomal and perianal ulceration**
- **Ulceration elsewhere on the face has not previously been reported**
- **Stopping nicorandil results in complete resolution of associated ulcers**
- **Patients with a complex medical history should prompt suspicion of iatrogenesis; the differential diagnosis should always include drug side effects**

Despite the ubiquity of nicorandil ulcers affecting the oral cavity and the perianal and perivulval skin, with recent reports also describing peristomal and surgical wound ulceration, to the best of our knowledge there have been no reports of ulcers affecting the nasal bridge or nasal dorsum. The presented case highlights the difficulties encountered in diagnosing a condition in a patient with a complex medical history, which diverted the physicians' attention away from the causative factor and resulted in a delayed diagnosis. Our patient's case emphasises the importance of maintaining a high index of clinical suspicion especially in patients with polypharmacy, as adverse drug reactions should always be considered in one's differential diagnosis.

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Address for correspondence:
Mr Fakhruddin Salim,
ENT Department,
3rd Floor, Southwark Wing,
Guy's Hospital,
Great Maze Pond,
London SE1 9RT, UK

E-mail: ruddin_79@yahoo.co.uk

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