Delayed diagnosis and inappropriate clinical management of nicorandil-induced oral lesions: A case report

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Oral ulcers have a number of causes, and as a result, their etiology can be difficult to determine. Clinical management can range from simple treatment of the symptoms to extensive surgical excision, as in the case of malignant ulcers. Nicorandil, an antiangina drug, has been identified as a potential trigger for cutaneomucosal ulcers. This article reviews the importance of taking a full medical history when seeking to identify the side effects of treatments. We present the case of a 70-year-old patient with chronic ulceration of the oral mucosa. Determining the cause of ulceration as a side effect of taking nicorandil was delayed because the team that initially managed the patient hypothesized a malignant etiology. As a result, a partial glossectomy was performed for diagnostic and therapeutic purposes. After extensive examination of the patient's medical history and current treatments, nicorandil was identified as the potential trigger. The patient finally recovered after discontinuation of nicorandil. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e324–e327)

Nicorandil is a coronary vasodilator, prescribed for the prophylactic treatment of angina. It has been used since 1984 and is generally indicated as a third-line treatment in patients not responding to calcium inhibitors or beta-blockers. Nicorandil is a nicotinamide ester (derivative of nicotinic acid), which causes both venous vasodilation by increasing the level of intracellular cyclic guanosine monophosphate and arterial vasodilation by triggering the opening of potassium channels. The opening of potassium channels, in combination with abnormally elevated levels of nicotinamide and nicotinic acid (metabolites of nicorandil) and pre-existing microlesions, is thought to cause ulcers in the buccal cavity.[1] Nicorandil-induced lesions were first described in 1997 by Reichert et al.[2]

The frequency of occurrence of ulcers in patients treated with nicorandil was estimated to be 5% by Marquart-Elbaz et al.[3] but only 0.2% by a group studying the impact of nicorandil on angina.[4,5] The ulcerating lesions that develop are painful; may be unique or multiple (1–10 elementary lesions); and are often deep and large in size (0.5–3 cm). Their borders are well defined and their base clean. These ulcers are preferentially located on the tongue and the inner cheeks. They may also be present on the gums and gingival crevices and, more rarely, on the lips and palate. The ulcers generally last for 3 weeks to 36 months, in a subintrant or chronic mode, with scarring or exacerbation. Progression is favorable within 1 to 12 weeks upon discontinuation of nicorandil treatment. Local treatment appears to be ineffective because the lesion is self-maintained by the continued intake of nicorandil. Any attempt at surgical excision of these lesions promotes an increase in local concentrations of nicorandil metabolites, thus maintaining the ulcers. General histologic analysis indicates only the presence of nonspecific inflammatory and necrotic tissue, although the appearance is distinct from cancerous ulcers.[3]

From a clinical point of view, drug-induced ulcers can have multiple diagnoses: cancerous lesions, aphthae, traumatic lesions, herpes lesions, syphilitic chancres, symptoms of other infectious or viral diseases, neutropenic ulcers, metabolic deficiencies (vitamins, ferritin, zinc), and so on.

Here, we describe a case of delayed diagnosis and erroneous treatment of oral ulcers in a patient treated with nicorandil.

CASE REPORT

A 70-year-old man was referred by his general practitioner to our department for disease of the oral mucosa. He had been suffering from painful recurring ulcers for over a year.

On the day of consultation at the department, the patient reported a history of type 2 diabetes treated with glimepiride; angina treated with bisoprolol, furosemide, candesartan, and nicorandil (40 mg/day); obliterating arteritis in the lower limbs; and cardiac rhythm disorders, for which he had been fitted with a defibrillator and a pacemaker. The patient also reported a history of alcohol and tobacco use, but on the day of consultation, he was no longer using either.

Successive treatment by his general practitioner, his dental surgeon, and an ear-nose-throat specialist had failed to cure or reduce his symptoms. Indeed, upon the appearance of the first ulcers, 1 year previously, drug-based treatment with fluconazole, valaciclovir,

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colchicine, and sodium bicarbonate mouth washes had been initiated, with the medical specialists considering a fungal, viral, or aphthous etiology. None of these treatments resulted in any improvement. Six months later, given the chronic nature of the symptoms and despite no evidence from cervicofacial tomodensitometry identifying a cancerous lesion, partial glossectomy was performed for diagnostic purposes, with excision of the sites of several ulcers. The histopathology results indicated a broad focus of nonspecific superficial ulcers, with no histologic markers of malignancy. Three months later, panendoscopy and biopsy of a lesion in the area joining the mobile tongue to the base of the tongue were performed. The results indicated an ulcerated mucosa with a fleshy lump, but still no histologic indications of malignancy. No other suspect lesions were found. Five months later, because of the previous ineffective treatments and the persistence of the painful lesions, the patient was referred to our department for his oral mucosal disease. During history, the patient described aphthous episodes lasting 3 weeks, followed by a 1-week remission. He did not have a history of aphthosis. On the medical history, the patient, his physician, and his dentist reported that all of the lesions leading to the surgical procedure were strictly the same (in form, size, etc.) as those observed during our consultation. Examination of the oral cavity revealed several elementary lesions. They measured greater than 1 cm along their long axis, with an erythematous contour and a supple base. The lesions were located on the mucosae of the upper lip, the lower vestibule, and the tip and dorsum of the tongue (Fig. 1, 2 and 3). Whitish and retracting healing lesions on the mucosae of the lower lip and the dorsum of the tongue, as well as the sequelae of the partial glossectomy, were visible (see Figure 3).

In the absence of extraoral ulcers, adenopathy, dysphagia, or other clinical, radiologic, or histopathologic indications of malignancy, the hypothesis that the ulcers were a side effect of the use of nicorandil was retained. The patient's cardiologist was consulted to consider changes to the patient's antiangina treatment. The cardiologist decided to eliminate nicorandil, without replacement therapy. One month after discontinuing nicorandil, the lesions disappeared completely; no relapse was recorded at 18 months.

DISCUSSION

The side effects of nicorandil are well known (in particular, skin and mucosal ulcers). Nevertheless, in the case presented here, a full year passed between the appearance of the first lesions and determination of the etiology of the ulcers.

In the case presented here, among the possible causes of oral ulcers, a traumatic origin (bite, irritation from dentures, sharp tooth edge, etc.) could be rapidly eliminated after examination of the oral cavity. If the ulcers corresponded to an outbreak of herpes, they would have presented a different appearance, with multiple, smaller ulcers; they would also have responded to treatment with valaciclovir. Similarly, the bilateral distribution did not suggest shingles. The utility of routine biologic examinations (blood count, search for deficiencies, and human immunodeficiency virus and syphilis tests) or tests to identify blood disease, infectious disease, or metabolic deficiency could be questioned. The hypothesis of (simple or complex) aphthosis can be retrospectively eliminated because of the resolution of the symptoms upon discontinuation of nicorandil. The most worrying diagnosis, suggested by the chronic nature of the lesions observed and their recurrence despite the various therapies tested, is that of a cancerous lesion (epidermoid carcinoma). However, the multiple biopsies and complementary examinations appeared to eliminate this hypothesis. Although the clinical appearance of the lesion could justify a second biopsy despite the negative results of the first, the complementary examinations and histopathologic analysis of the panendoscopy specimens should

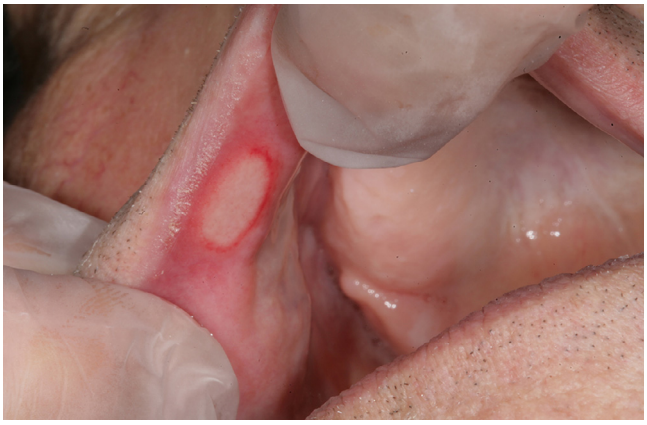

Fig. 1. Oral ulcer on the mucous membrane of the upper lip.

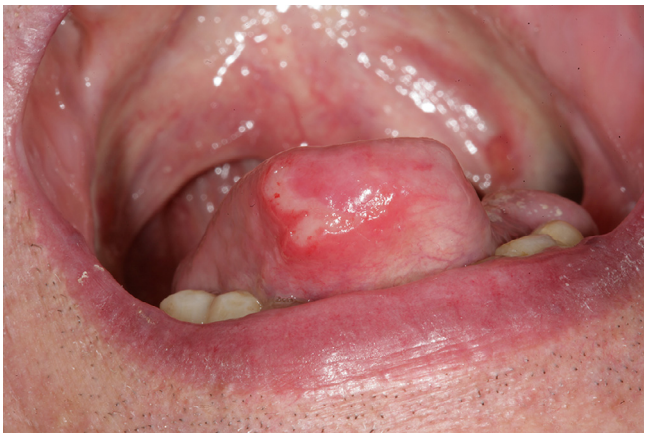

Fig. 2. Ulcer on the tip of the tongue.

have led the clinicians to seek an alternative etiology. Understandably, they wished to first eliminate the most serious etiology for the oral ulcers. However, in this instance, the medical team was unaware of the real cause while looking for a cancerous origin. In fact, with biopsy and the confirmed anatomopathology result ruling out a cancerous etiology, other causes should have been investigated. An irreversible mutilating surgical procedure should only be undertaken if it offers proven benefit, which was not the case here. The clinical re-examination of the lesions should have revealed that the multiple, recurrent, superficial lesions did not present any sign of malignancy. This proved to be a disadvantage for the patient because it delayed identification of the true etiology of these lesions and resulted in his undergoing a mutilating partial glossectomy.

With regard to the physiopathology of nicorandil-induced ulcers, although the role played by nicotinamide appears to be a determinant, other factors,[6] including an immunoallergic or toxic reaction; predisposition (pre-existing lesions, history of aphthosis, etc.); a role played by accessory salivary glands and potassium channels; or an effect of polypharmacy, have also been suggested. In our case, the patient was also treated with glimepiride (oral antidiabetic); candesartan (angiotensin II receptor antagonist); and bisoprolol (beta-blocker), for which also there are reports in the literature of cases where ulcers were induced.[7] Although the lesions were cured after the patient discontinued nicorandil, the implication of this drug alone in the appearance of ulcers could be debated in the context of multiple treatments.

It is essential that the side effects of drugs be communicated to pharmacovigilance centers. The appearance of ulcers linked to nicorandil in the case reported here was, of course, reported to the appropriate body. In 2000, Boulinguez and Bonnetblanc reported a 2-year lag between commercialization of nicorandil in France (1994) and the first reports of associated ulcers to the pharmacovigilance centers (1996).[8] On the basis of the numerous reports in France subsequently, in 2012, the French Health Products Safety Agency (ANSM) sent a letter warning health care professionals that nicorandil can induce mouth ulcers as a side effect.[9]

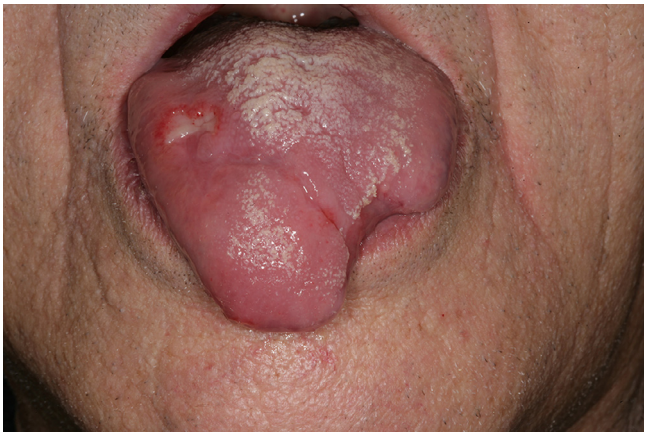

Fig. 3. Ulcer of the right dorsal tongue, and sequelae of the partial glossectomy performed on the left side.

The dose of nicorandil appears to have a nonnegligible impact on the occurrence of ulcers. Ulcers generally occur over the first year of treatment and/or after a dose increase[5] or when the maximum recommended dose (40 mg/day) is exceeded,[10] although some cases have been reported several years after start of treatment.[7] As an example, few cases have been reported in Japan, where usual daily dose is 15 mg/day.[11] In the case presented here, the patient was taking 40 mg/day. Thus, a dose reduction for this patient could have been considered, rather than a complete discontinuation of the treatment. Alternatively, another antiangina agent could have been substituted for nicorandil. Indeed, in 2015, the ANSM recommended prescription of nicorandil for "treatment of stable angina only in patients who are insufficiently controlled or present a contraindication or intolerance to first-line antiangina treatments, such as beta-blockers and/or calcium antagonists" at a usual dose of 20 to 40 mg/day in 2 doses, always with progressive introduction and discontinuation of treatment if ulcers appear (wherever they are located) and referral to a cardiologist for treatment adjustment.[12]

The appearance of nicorandil-induced ulcers has also been suggested to correlate with patient age[6] and weight.[13] In our case, the patient's weight was 72 kg and height 1.70 m, ruling out an excess dose.

Finally, Pisano et al.[10] reported no correlation between nicorandil dose and duration of ulcers. In our patient, despite the maximum recommended dose being taken, lesions occurred over 3 weeks, with a single week of remission.

In addition to oral lesions associated with nicorandil, other lesions have also been reported[6,14]: cutaneous, anal, gastrointestinal, colitic, peristomal, penile, vaginal, and ocular lesions. No lesions were observed at any other sites in the present case.

CONCLUSIONS

This case is a reminder of the importance of obtaining the patient's full history when attempting to diagnose diseases of the oral mucosa, in particular those related to drugs likely to induce oral side effects. In the present case, a well-conducted initial consultation would readily have led to earlier identification of the etiology and obviated the need for numerous tests, particularly the unnecessary mutilating surgical intervention.

PRESENTATION

This case report was presented as communication at the French Society of Oral Surgery congress, 2016, in Metz, France.

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