Fixed Drug Eruption on the Tongue Due to Naproxen

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Fixed drug eruption (FDE) is a delayed cutaneous hypersensitivity reaction characterized by recurrent, well-defined lesions at the same location on the skin and/or mucous membranes upon readministration of the causative drug. Solitary bullous FDE of the tongue is a very uncommon finding and remains a diagnostic challenge [1-3].

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) derived from propionic acid that is widely used for symptomatic relief of painful disorders such as headache. We report a rare case of naproxen-induced isolated bullous FDE.

A 46-year-old woman with a medical history of migraine-type headache, was treated with naproxen. Two days later, she developed a painful, large ulcer on the tongue. The physical examination was unremarkable, with the exception of a well-defined bullous/erosive oval lesion measuring 5 cm × 3 cm on the right posterior dorsum of the tongue, with multiple pinhead-sized vesicles (Figure). No other mucosal or cutaneous involvement was observed. A complete blood count showed normal results. The patient reported a previous episode at the same site about 2 months earlier, also following intake of oral naproxen. Since this first episode, she had taken other NSAIDs, such as ibuprofen or nimesulide, with no subsequent reactions. Based on the physical examination and the patient's clinical and medication history, naproxen-induced FDE was suspected. The patient was advised to avoid naproxen. The lesion improved without complications within 2 weeks of discontinuation of the offending drug. In addition, given that the lesion was uncomfortable, the patient administered systemic corticosteroid and beclomethasone dipropionate ointment twice daily. However, on the first day of the next migraine-type headache, the patient took naproxen again. Four hours later, multiple blisters reappeared at the same site on the tongue. The blisters ruptured within 1 day, resulting in an irregular erosion on the right dorsal surface of the tongue (approximately 5 cm in the longer diameter), similar to the 2 previous presentations (Supplementary Figure). No other intraoral or extraoral lesions were present. Histopathology of an incisional biopsy from the margin of the tongue revealed necrosis of epidermal keratinocytes and mild hydropic degeneration of the basal layer and mixed inflammatory infiltration at the dermoepidermal junction, with a predominance of neutrophilic and mononuclear cells. The picture was consistent with FDE. Application of the Naranjo algorithm yielded a causality score of 11, thus indicating that the patient had experienced a definitive reaction to naproxen. No further occurrences of the lesion were observed after discontinuation of the drug.

The literature contains very few reports on oral FDE, in particular that induced by naproxen. Özkaya [4] found oral mucosal lesions (excluding the lips) in 61 of 176 (35%) cases of FDE. Isolated oral mucosal involvement was found in only 9 of the 61 patients (15%). In this study, solitary bullous/erosive lesions of the dorsal tongue were almost exclusively

Figure. Multiple blisters on the tongue.

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induced by trimethoprim-sulfamethoxazole. The study by Özkaya included the only case of FDE affecting the dorsum of the tongue in the literature.

A correct diagnosis of solitary bullous/erosive lesions of the tongue due to FDE is challenging because of the wide spectrum of differential diagnostic conditions, including herpes simplex virus infection, oral candidiasis, erythema multiforme, syphilis, and autoimmune blistering disorders such as pemphigus vulgaris and Behçet disease [1-3]. In the absence of additional skin involvement, the location and morphology of the oral mucosal lesion, a history of site-specific flares and the interval between exposure to the causative agent and reactivation of old lesions within minutes to several hours could be highly suggestive of FDE. The definitive diagnosis should be based on histopathology.

Topical provocation testing can be performed at the sites of previous lesions, as the results depend on the activation of intraepidermal $CD8^+$ memory T cells in these areas, although the false-negative rate is high [6]. Therefore, oral provocation testing is the gold standard for identifying the causative drug in FDE. This approach is safe and highly sensitive and specific and remains the most reliable method for the diagnosis of FDE [1-5]. However, it may point to generalized bullous lesions in some cases.

The management of FDE primarily involves discontinuation and avoidance of the offending drug. Depending on the extent and severity of the lesions, topical or systemic corticosteroids may be prescribed. Although cross-reactivity between drugs with similar molecular structures is possible, Gonzalo et al [7] did not find cross-reactivity between naproxen and other propionic acid derivatives. Similarly, in the case reported here, the patient tolerated other NSAIDs, including ibuprofen (propionic acid derivative).

In the present case, the definitive diagnosis of FDE was based on a high index of suspicion, a detailed medication history, recurrent oral lesions, the clinical course, histopathology, and positive involuntary oral provocation with naproxen. FDE should be suspected in patients with recurrent oral ulcerations at the same site after administration of naproxen. Discontinuation of the offending drug and use of an appropriate alternative drug are necessary to ensure healing and avoid recurrence.

The present case also illustrates the importance of recognizing unusual presentations of adverse drug reactions as a key skill for the allergist.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Figure. An ulcer on the dorsum surface of the tongue.

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