

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 of skin and/or mucous membranes upon re-administration of the causative drug. Solitary bullous FDE of the tongue is very uncommon finding and remain a diagnostic challenge [1-3].

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

CASE REPORT: A 46-year-old female with a medical history of migraine-type headache, was treated with naproxen and two days later developed a painful, large ulcer on the tongue. Examination was unremarkable with the exception of welldefined bullous/erosive oval lesion of 5cm x 3cm, on right posterior dorsum of the tongue, with multiple pinhead-sized blisters (Figure 1). No other mucosal or cutaneous involvement was observed. A complete blood count showed normal results. The patient reported a previous episode on the same site of the tongue about two months earlier, also following naproxen oral administration. Since this first episode, other NSAIDs were taken, such as ibuprofen or nimesulide, without complication. Based on the physical examination as well as the patient's medical and medication history, FDE due to naproxen was suspected. The patient was advised to avoid naproxen. Lesion improved without complications in 2 weeks with discontinuation of the offending drug. In addition, given the disturbance of the lesion, to relieve the burning sensation, systemic glucocorticoid

and beclomethasone dipropionate ointment twice daily were administered. However, on the first day of the next migraine-type headache, the patient took again naproxen. Four hours after, multiple blisters reoccurred on the same site of the tongue. The blisters broke within 1 day, resulting in an irregular erosion on the right dorsal surface of tongue, measuring approximately 5 cm in greatest diameter, similar to previous two presentations (Supplementary Figure). No other intraoral or extraoral lesions were present. Incisional biopsy was obtained from the margin of tongue. The histopathology assessment showed necrosis of epidermal keratinocytes and mild hydropic degeneration of basal layer and mixed inflammatory infiltration in the dermoepidermal junction with neutrophilic and mononuclear cells predominance. The picture was consistent with FDE. Applying Naranjo's algorithm, a causality score of 11 was obtained and was categorized as definitive reaction to naproxen. With avoidance, no more recurrent tongue lesions occurred.

There are very few reports in the literature on oral FDE, in particular caused by naproxen. Özkaya [4] found oral mucosal lesions (excluding lips) in 61 of 176 (35%) cases of FDE. Only 9 of 61 (15%) had isolated oral mucosal involvement. In this study, solitary bullous/erosive lesions of the dorsal tongue were almost exclusively induced by trimethoprim-sulfamethoxazole. The only case of FDE on the dorsum of the tongue referred in the literature is included in the Özkaya study [4].

A correct diagnosis of FDE solitary bullous/erosive lesions of the tongue is challenging because of the wide spectrum of differential diagnostic conditions, including herpes simplex virus infection, oral candidiasis, erythema multiforme, syphilis, or autoimmune blistering diseases such as pemphigus vulgaris and Behçet's disease [1-3]. In the absence of additional skin involvement, the location and morphology of the oral

mucosal lesion, history of site-specific attacks, time interval between exposure to causative agent and reactivation of old lesions within minutes to several hours, might be highly suggestive of FDE. In addition, histopathological examination can differentiate the diagnosis.

Topical provocation can be performed at the sites of previous lesions, as the results depend on the activation of intraepidermal CD8+ memory T cells at these sites, but the false-negative rate is high [6]. Therefore, oral provocation challenge is the gold standard for identifying the causative drug in FDE, it is a safe and still the most reliable method for the diagnosis of FDE with a high sensitivity and specificity [1-5]. However, it may lead to generalized bullous lesions in some cases.

The management of FDE primarily involves drug discontinuation and avoidance of the offending drug. Depending on the extent and severity of the lesions, this may be supplemented with topical or systemic steroids. Although cross-reactivity between drugs with similar molecular structures is possible, in a previous study, cross-reactivity between naproxen and other propionic acid derivatives was not found [7]. Like, in the case reported here, the patient tolerated other NSAIDs included ibuprofen (propionic acid derivative).

In our case, a high index of suspicion, detailed medication history, recurrent oral lesions, course of the symptoms, histopathology in addition to a positive involuntary oral provocation with naproxen were crucial for definitive diagnosis of FDE. FDE should be suspected in a patient with recurrent oral ulcerations at the same site after

naproxen administration. Discontinuation of offending drug and use of an alternative appropriate drug is required to achieve healing and avoid recurrence.

This case also illustrates the importance of recognizing unusual presentations of adverse drug reactions as an important skill for the allergist.

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Conflicts of Interest

All authors have no conflicts of interest to declare.

Authorship

CF, TC, AG and designed the study and wrote the manuscript. CF and AG performed interpretation of the results.

All authors read and approved the final manuscript.

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Figure 1. Multiple blisters on the tongue

