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Nortriptyline-induced oral ulceration: A case report

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Abstract

Drug-induced oral ulcers are lesions of the oral mucosa accompanied by painful symptoms, such as burning mouth, metallic taste, dysgeusia, or ageusia. This report demonstrates the first documented case of drug-induced oral ulcers with the tricyclic antidepressant nortriptyline. In this case, a 49-year-old female initiated treatment for refractory neuropathy with nortriptyline. Within 2 weeks of therapy, painful, oral, bubble-like ulcers developed. Complete symptom resolution occurred approximately 1 month after discontinuation of nortriptyline. Clinicians should be cognizant of nortriptyline's ability to potentially induce oral ulcers; however, the exact mechanism for this adverse event is unknown.

Keywords: nortriptyline, oral ulcer, neuralgia, oral, cobicistat

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Background

Drug-induced oral ulcers are lesions of the oral mucosa accompanied by painful symptoms. The underlying mechanism is often unclear, but possible causes include local irritants or the effects of systemic drugs.[1] Common symptoms experienced from pharmacologically induced lesions include burning mouth, metallic taste, and dysgeusia or ageusia.[2] A correlation between the time of ulcer development and the initiation or dose titration of a pharmacologic agent can further implicate a drug-related adverse effect. Drug-induced oral ulcers may improve with conventional treatments, such as corticosteroids, but definitive management is dependent on discontinuation of the offending agent.[1]

Nortriptyline is a secondary amine tricyclic antidepressant (TCA) that increases synaptic concentrations of serotonin and norepinephrine in the central nervous system by reuptake pump inhibition. Inhibition of H_1-histaminic, $\alpha 1$-adrenergic, and muscarinic cholinergic activity has also been observed. Nortriptyline is currently Food and Drug Administration approved for the treatment of depression.[3] Off-label uses include the following: chronic pain, diabetic neuropathy, myofascial/orofacial pain, postherpetic neuralgia, nocturnal enuresis, neurogenic bladder, and attention deficit hyperactivity disorder.[4] Side effects of nortriptyline as well as other TCAs include sedation; orthostatic hypotension; anticholinergic symptoms; gastrointestinal symptoms, such as nausea and vomiting; sexual dysfunction; and allergic reactions, such as skin rash, urticaria, and itching.[3,4]

Although many medications are known to be causative agents of oral lesions, including nonsteroidal anti-inflammatory drugs and cytotoxic medications, there are few cases of antidepressant medication–induced lesions.[5] Based on review articles,[6,7] the only TCA with documen-

tation of being a possible causative agent for both dysgeusia and oral ulcerations is imipramine. This report, to our knowledge, demonstrates the first documented case of drug-induced oral ulcers with the TCA nortriptyline.

Case

This case describes a 49-year-old female with a past medical history significant for human immunodeficiency virus (HIV) diagnosed 24 years ago, hypertension, hyperlipidemia, constipation, and neuropathy and a past surgical history significant for umbilical hernia repair. Her most recent HIV viral load was undetectable with a HIV RNA level <20 copies/mL and has had CD4+ T-cell counts consistently >500 cells/mL. Initially, she presented to an HIV-specialized primary care clinic with a chief complaint of refractory neuropathy. The pain and burning she experienced started in both feet 2 years prior. The pain was predominantly in the dorsum of her feet with some involuntary cramping and twitching of her toes and calves. The pain and dysesthesias were worse when she sat or lied down but improved upon ambulation. For management of her refractory neuropathy, she was referred to a neurologist. At the time of the neurology visit, the current medication list included elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate 150/150/200/25 mg by mouth daily, rosuvastatin 5 mg by mouth daily, ferrous sulfate 325 mg by mouth twice daily, metoprolol succinate 25 mg by mouth daily, gabapentin 100 mg by mouth twice daily, and aspirin 81 mg by mouth daily. Previous failed pain management therapies included acetaminophen, duloxetine (patient developed tardive dyskinesia), pregabalin (unknown daily dose), lidocaine/pilocarpine 2.5%/2.5% topical cream applied to both feet twice daily, and gabapentin 100 mg by mouth twice daily (patient complained of drowsiness). She did not tolerate further dosage increases with pregabalin or gabapentin. Lidocaine 5% patch and a similarly compounded cream also failed to provide the patient with any relief. At this visit, the patient was diagnosed with HIV-related small fiber neuropathy and prescribed nortriptyline, starting at 10 mg by mouth at bedtime with instructions by her neurologist to titrate by 10 mg weekly to a target dose of 80 mg/d.

One week after initiating nortriptyline, her dosage increased (as instructed) from 10 mg to 20 mg once daily at bedtime. She started to notice painful, bubble-like ulcers forming in her mouth. Because she had some transient improvement in her symptoms, she chose to continue therapy due to numerous failed past treatments. By weeks 4 and 5, the oral ulcers had become white and inflamed and spread to her cheeks, gums, and front of her mouth. She also began to experience dark purple lesions on her tongue and was unable to eat due to the pain. The oral ulcerations remained intact and steadily increased in size, number, and sensation of pain with each weekly dosage increase. By week 8, regardless of the patient experiencing moderate benefit, the ulcers were so severe she requested to stop therapy with nortriptyline. The neurologist was the only health care provider to evaluate the ulcers at which time prednisone 10 mg by mouth daily for 5 days was prescribed. The corticosteroid provided minor relief in pain but no change in ulcer formation. At this time, she was instructed to taper the nortriptyline by 10 mg/wk until discontinuation. The neurologist elected to choose a slow taper due to the possibility of nortriptyline not being the causative agent and the only treatment that had shown therapeutic benefit (Figure).

Over the course of the 8-week taper, the ulcers progressively improved as well as her symptoms. During a follow-up phone call 1 month after discontinuation of nortriptyline, she stated she was still experiencing pain and discomfort when eating hot or spicy food. At a follow-up phone call 1 month after discontinuing nortriptyline, her oral ulcers completely resolved.

Discussion

The case presented involved a woman with multiple oral ulcerations after starting nortriptyline therapy. She was concerned about the ulcer formation but initially was willing to continue therapy due to the transient relief of her HIV-related small fiber neuropathy. The differential diagnoses for the cause of the oral ulcerations considered by the medical team were medication- or disease-induced.

Infection with HIV causes immunosuppression, which increases the relative risk of developing acute and chronic oral ulceration.[8] These HIV-related oral ulcers are generally viral, bacterial, or fungal in origin. However, it is unlikely the ulcers that developed in this patient were HIV related because the patient's HIV viral load was well suppressed and the patient consistently had a high CD4+ T-cell count. This is suggestive of robust immune function, further decreasing the likelihood of an HIV-related infection as the cause of the oral ulcerations. Independent of the patient's HIV infection, other viruses can cause oral ulceration. Herpes simplex virus (HSV) 1, HSV2, and Epstein-Barr virus can all cause different variations of oral ulcerations.[9] The TCA amitriptyline is known to inhibit acid sphingomyelinase, an enzyme responsible for the mediation of leukocyte function and homeostasis potentially affecting immune function. In theory, due to the structural similarity with nortriptyline, this agent may

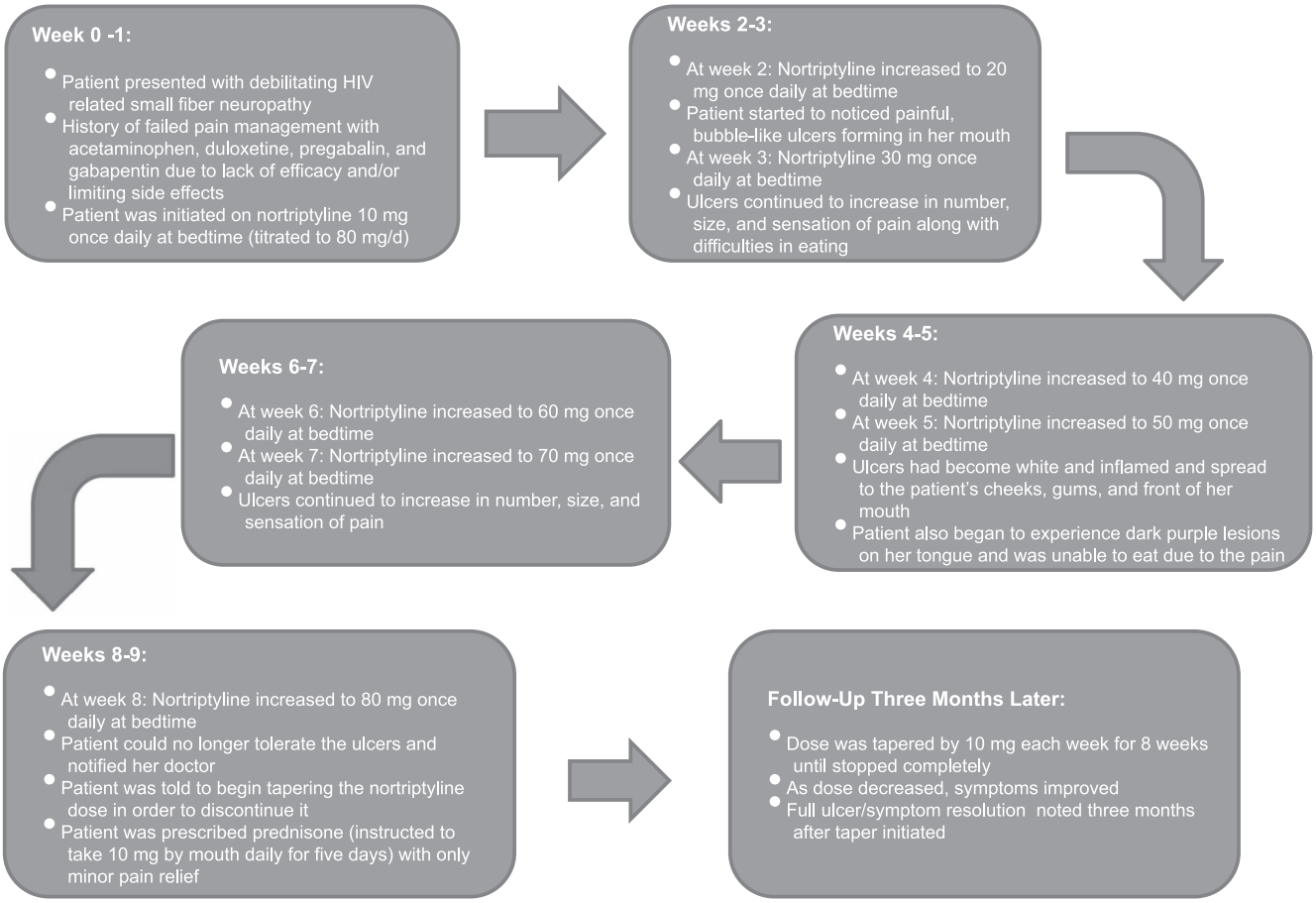

FIGURE: Timeline of nortriptyline-induced ulcer progression and symptom resolution

increase the risk of developing oral ulceration and/or could reactivate quiescent HSV.[10] These etiologies are unlikely due to the patient denying systemic signs or symptoms of infection but cannot be ruled out entirely.

The timing of nortriptyline initiation to oral ulceration development as well as the timing of nortriptyline discontinuation to ulceration resolution implicate the adverse effect as being nortriptyline-induced. When assessing the likelihood of a medication-related adverse event using the Naranjo Nomogram for Assessment of Adverse Drug Reactions, the score was 4, indicating a possible relationship between nortriptyline initiation and the oral ulceration development.[11] There is a potentially weak drug interaction between nortriptyline and the antiretroviral therapy, further increasing the likelihood of an adverse event caused by nortriptyline. Coadministration with cobicistat, a protease inhibitor and weak inhibitor of CYP2D6, may increase concentrations of nortriptyline, a CYP2D6 substrate.[12] This combination has not been studied, but careful dose titration of nortriptyline and monitoring for antidepressant response is recommended by the package insert.[13] Unfortunately, no nortriptyline levels were able to be drawn to assess for potentially supratherapeutic levels.

Conclusion

To date, there have been no previously reported cases of nortriptyline-induced oral ulcers. In this case report, a temporal relationship was observed between the initiation of nortriptyline and the development of oral ulcers. Furthermore, due to a CYP-mediated drug interaction between the antiretroviral therapy and nortriptyline, it is possible increased concentrations of nortriptyline were experienced, potentiating this adverse event. Clinicians should be cognizant that the use of nortriptyline may result in oral ulcers, especially in individuals with immunosuppressing comorbidities or taking antiretroviral therapy containing protease inhibitors.

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