Case Report

Trigeminal Zoster with drug-induced labial angioedema leading to necrosis

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Abstract

Introduction. Zoster is caused by the reactivation of a dormant viral infection, and is characterized by painful, vesicular lesions along a dermatome. Neuritic pain associated with zoster can be treated with anticonvulsant medications.

Case Report. An immunocompetent adult physician developed prominent zoster lesions in the trigeminal nerve distribution. Treatment included antiviral therapy for the acute infection, and pharmacotherapy for neuritic pain. Pharmacotherapy included several anticonvulsant agents, with labial angioedema developing after initiation of oxcarbazepine.

Discussion. The case is notable for the pictorial timeline of lesion development, as well as the marked incident angioedema following initiation of treatment for neuritis with oxcarbazepine.

Conclusions. Clinicians should remain vigilant for drug-induced facial angioedema when treating patients with trigeminal zoster-related neuritis due to the potential for angioedema to aggravate a lesion, resulting in scarring. Angioedema of the head and neck should be closely monitored due to the potential for airway compromise.

Keywords: Zoster, varicella, angioedema, oxcarbazepine, adverse drug reaction

Introduction

Varicella zoster virus (VZV) infection manifests in two disease forms. The initial VZV infection, called varicella or chickenpox, is characterized by disseminated skin lesions, fever, and malaise that often resolves within 10-14 days. After resolution of the initial infective symptoms, VZV can lie dormant in sensory ganglia until reactivation. The reactivated infection - called zoster or shingles - features painful, vesicular, unilateral skin lesions along a distinct dermatomal distribution [1].

The management of zoster includes treatment of the acute viral infection, and the treatment of acute pain associated with the acute neuritis. The initiation of antiviral treatment within 72 hours of vesicular eruption can reduce the intensity and duration of the painful episode [1]. Valacyclovir and famcyclovir are considered first-line antiviral treatments based on efficacy and ease of dosing [2]. Mild acute neuritic pain can be managed with NSAIDs and acetaminophen; severe pain can also be treated with short courses of steroids and opioid analgesics. In patients for whom these interventions are insufficient, anticonvulsant medications may be useful. These agents may include gabapentin, tricyclic antidepressants (e.g., nortriptyline), carbazepine, and/or oxcarbazepine.

The aim of this case presentation is to describe a drug-induced exacerbation of an extant facial zoster lesion resulting in long-term scarring. The objective of this case report is to highlight the potential for medication-related disease complications unique to zoster-related trigeminal neuritis.

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Case Report

Disclosure: the author is the patient, and waives anonymity.

A 36-year-old immunocompetent male physician was seen in an outpatient clinic after the left middle and lower thirds of his face erupted with painful vesicles; intraoral lesions also appeared in the left cheek mucosa. The lesions appeared following several days of left-sided head and face pain. Skin examination showed lesions corresponding to the maxillary (V2) and mandibular (V3) branches of the left trigeminal nerve. Oral examination showed ulcerated oral mucosa in the left cheek without tongue lesions or thrush. Eye exam showed no evidence of ophthalmic (V1) branch involvement.

His medication regimen was sertraline 100 mg qd for anxiety in sustained remission for over a decade. All immunizations were up to date and the patient had chicken pox at age 6. He had no known drug allergies or immune dysfunction. The patient's past medical history was notable for long-term gastroesophageal reflux for which he had undergone a Nissen fundoplication 2 months prior to vesicular eruption without complication. There were no known immunity-related conditions in the patient's family history.

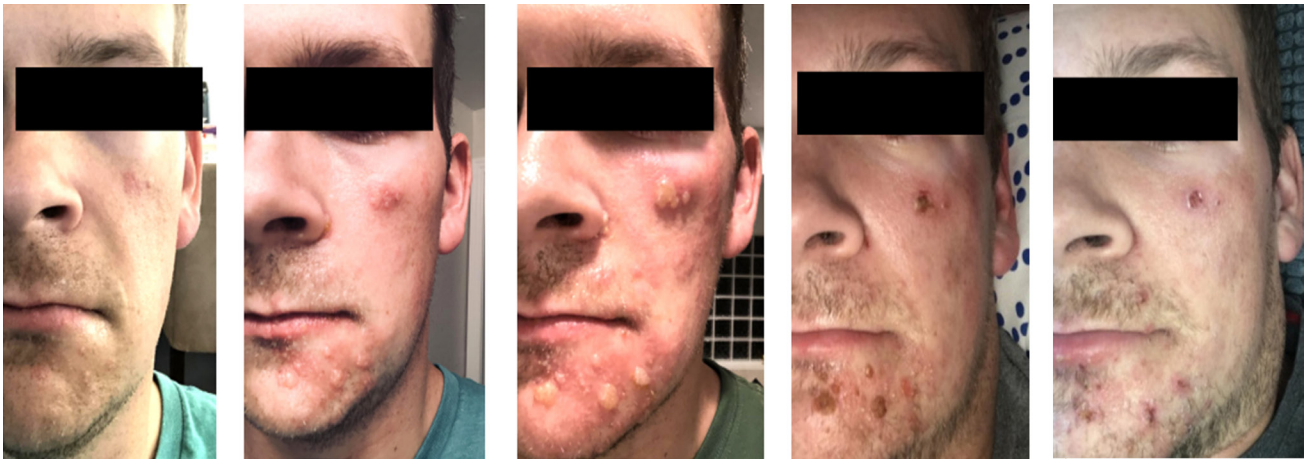
Comprehensive metabolic panel and complete blood count were notable for a WBC 10.9 x10^3/microliter with lymphocytic predominance.

The patient was diagnosed with trigeminal zoster with neuritis and prescribed valacyclovir (VAL) 1g PO q8h x7d and gabapentin (GAB) 600 mg PO q8h (Figure/Table 1a). He also received viscous lidocaine (LID) 2% for oral lesions as needed q4-6h. Corticosteroids were not used based on provider preference and concern for superinfection. Seven days after lesion appearance, persistent facial pain prompted initiation of baclofen (BAC) 10 mg PO q8h and nortriptyline (NOR) 25 mg PO q12h. Three days later, oxcarbazepine (OXC) 150 mg PO q12h was added to the pain regimen as well.

Within 24 hours of starting OXC, the patient developed incident angioedema of the lower lip (Figure/Table 1b). The angioedema worsened, aggravating a zoster lesion at the base of the lip. The lesion ultimately underwent focal necrosis. On Day 13, only OXC was discontinued from the regimen; symptoms improved over the next several days with diphenhydramine (DIP) 25mg q12h for swelling. All zoster lesions resolved over the next 3 weeks; however, the lower lip necrosis created a scar that persists 2 years following the episode.

The report's author is the patient.

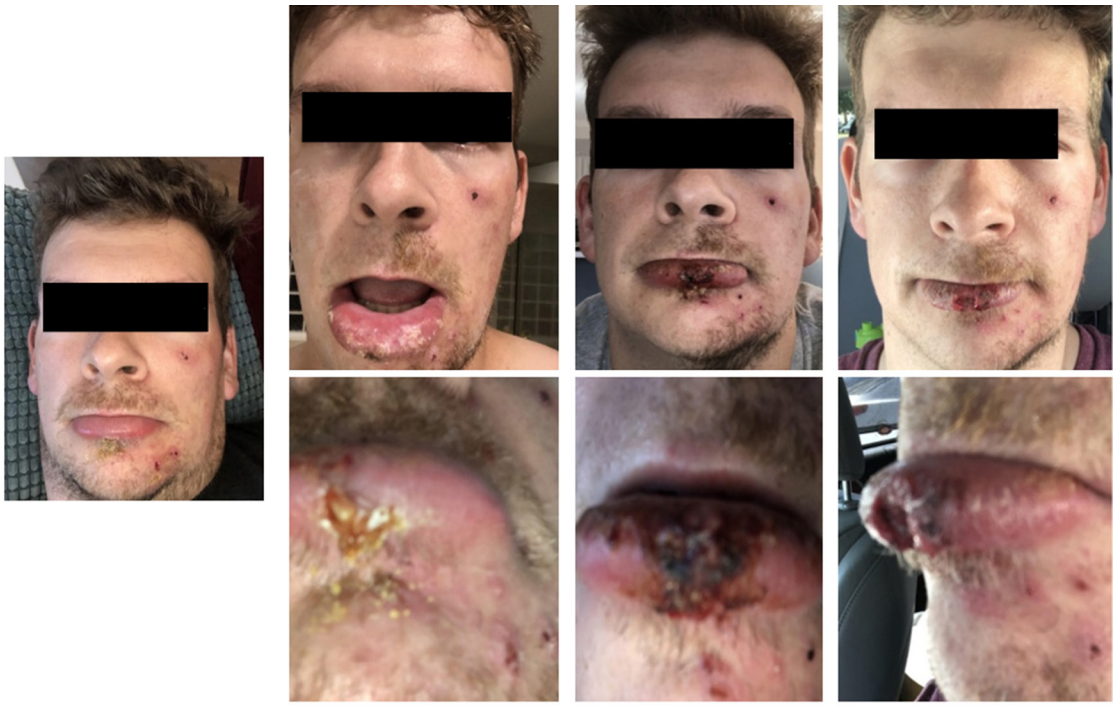
Figure/Table 1a. Temporal Evolution of V2/V3 Zoster Lesions with Medications: Valacyclovir (VAL), Gabapentin (GAB), Baclofen (BAC), Nortriptyline (NOR).



Day 1*	2	4	7	10
VAL	VAL	VAL	VAL	GAB
GAB	GAB	GAB	GAB	BAC
LID	LID	LID	BAC	NOR
			NOR	

*Day 1: Lesion appearance.

Figure/Table 1b. Temporal Evolution of Labial Angioedema with Medications: Valacyclovir (VAL), Gabapentin (GAB), Baclofen (BAC), Nortriptyline (NOR), Oxcarbazepine (OXC), Diphenhydramine (DIP).



OXC Start **OXC End**

Day 11*	12	13	15	16
GAB	GAB	GAB	GAB	GAB
BAC	BAC	BAC	BAC	BAC
NOR	NOR	NOR	NOR	NOR
OXC	OXC	DIP	DIP	DIP

*Day 1: Lesion appearance; OXC – Oxcarbazepine.

Discussion

VZV reactivation is common, estimated to affect nearly 1 in 3 adults in their lifetime [3]. Zoster vaccines reduce the incidence of zoster reactivation and postherpetic neuralgia. Age is the most important risk factor for the development of zoster, with patients aged >50 years at highest risk [3]. Additional risk factors include immunocompromise [5], female sex [6], and Caucasian race [7]. Psychological stress has been hypothesized to be a risk factor for VZV reactivation; however, this hypothesis has not been validated [8].

Additionally, this case highlights an adverse drug reaction, angioedema, soon after starting oxcarbazepine for neuritis. Angioedema is localized subcutaneous swelling due to fluid extravasation into interstitial tissues. Angioedema is broadly classified into two categories: mast cell-mediated and bradykinin-mediated [8]. Mast cell-mediated angioedema is a type I histamine-mediated hypersensitivity reaction, and is the likely etiology of the symptoms for this patient. This process is acute, featuring urticaria treatable with antihistamines and corticosteroids [9]. Drug-related bradykinin-mediated angioedema is typically associated with ACE inhibitors, progresses more gradually than the histamine-mediated process, and lacks urticaria. Corticosteroids and antihistamines are ineffective treatments for bradykinin-mediated angioedema. In this case, coupling diphenhydramine with discontinuation of the drug causing the symptoms – suspected to be oxcarbazepine – were effective interventions for the patient.

The pharmacologic activity of oxcarbazepine is exerted through the 10-monohydroxy metabolite of the drug [10]. This metabolite blocks voltage-sensitive sodium channels, increases potassium conductance, and modulates the activity of high-voltage activated calcium channels. Common side effects of oxcarbazepine include dizziness, drowsiness, headache, diplopia, and gastrointestinal

symptoms. The FDA-approved label acknowledges "[r] are reported cases of angioedema" following initiation of oxcarbazepine and recommends patients who experience angioedema in the lips, eyelids, glottis, or larynx to discontinue the medication without rechallenge. A review of pediatric angioedema cases associated with oxcarbazepine reported to the FDA MedWatch program database in the first 6 years of the drug's approval (2000-2006), identified 9 cases with variable time to onset of angioedema following exposure. All patients were reported to experience a full recovery following discontinuation of the product [11].

The labial angioedema in this case was likely caused by oxcarbazepine using the WHO-UMC classification system of case causality [12]. This is based on a reasonable temporal connection between drug exposure and event, with clinically reasonable response to drug withdrawal, and reaction unlikely to be caused by the underlying disease or other drugs. Gabapentin, nortriptyline, and baclofen are all capable of causing angioedema; however, these medications were all continued when oxcarbazepine was discontinued, and the angioedema resolved.

The patient in this case does not fit the typical profile of someone at risk for VZV reactivation: he is young, male, and immunocompetent. The zoster vaccines marketed in the USA are recommended for patients aged >50 years, and no approved zoster vaccine would have been recommended in this patient based on his age [3]. In the absence of known risk factors, this patient's reactivation is idiopathic – though potentially related to stress following abdominal surgery requiring 4 weeks of a liquid diet and 20 pounds of weight loss. The patient's profession as a physician prompted the capture of a pictorial record of VZV lesion progression in the V2/V3 nerve distribution, which is not commonly visualized in medical resources.

Conclusions

Clinicians should remain vigilant for adverse drug reactions related to the use of agents for acute neuritis in patients with trigeminal zoster due to the potential for angioedema-related aggravation of facial zoster lesions. If angioedema occurs in patients with zoster treated with anticonvulsant agents, providers should establish a detailed timeline of medication exposure to identify and remove the suspected causative agent. Angioedema of the head and neck carries the risk of airway compromise and medical emergency.

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