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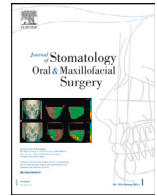
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Letter to the Editor

Zoster sine herpette of the trigeminal nerve revisited as a COVID-19-associated disease: Atypical manifestation of herpes zoster masquerading odontogenic symptoms

During the COVID-19 pandemic, epidemiologic and clinical evidence of COVID-associated diseases such as herpes zoster (HZ) has been accumulated [1]. HZ is associated with risk factors such as older age, female sex, mechanical trauma, recent psychological stress, and immunosuppression [2]. Notably, the T-cell immune system is suppressed in COVID-19 patients [3], who are thus considered to be at an increased risk of HZ [4]. HZ typically affects the trunk, but it also affects the trigeminal nerve in 20% of cases [5,6], mostly in the ophthalmic branch and rarely in the mandibular branch [7].

An atypical variant without vesicular eruption, known as zoster sine herpette (ZSH), has posed a diagnostic challenge for clinicians [8]. In enteric neurons, varicella-zoster virus (VZV) reactivation can induce inexplicable abdominal pain and impaired gastrointestinal function with no cutaneous manifestations (enteric ZSH). In the maxillofacial region, ZSH provokes neuropathic orofacial pain as a prodromal and the following acute symptom and rarely accompanies even complications such as encephalitis or stroke, with a potentially fatal outcome if ZSH is overlooked [9]. The reactivation may also develop as peripheral facial palsy of ZSH in a form indistinguishable from Bell's palsy. Improvement of ZSH with painful facial palsy requires a longer period than other peripheral palsies such as Bell palsy due to other causes and Hunt syndrome without skin lesions [10]. Mandibular ZSH often manifests with predominant odontogenic symptoms such as toothache and gingival swelling in the acute phase, which can lead to misdiagnosis and inappropriate dental treatment. We hereby present the first case of COVID-associated trigeminal ZSH.

A lactating 32-year-old Japanese woman presented with toothache of the right lower molars radiating to the retromolar region (Fig. 1). Five weeks prior to consultation, the patient had COVID-19 and was symptomatically treated at home. There were no episodes of oxygen desaturation, although she was febrile for a week, followed by persistent cough and fatigue for two weeks. Two weeks prior to consultation, she experienced right-sided ear ache and constricting pain in the posterior mandible, thereby prompting referral to an otolaryngologist. The pain was refractory to the administration of antibiotics and acetaminophen. The patient reported a previous episode of chickenpox at a younger age and received the COVID-19 vaccination twice more than half a year ago. During the initial visit, the patient had unilaterally reduced sensation of the chin and buccal skin, as well as an itching sensation on the intraoral mucosa, including the right side of the tongue and lower molar gingiva. There was no impairment of

facial muscle movement or facial skin vesiculation. Oral examination revealed a slightly swollen lower lip and no vesicular eruptions on the mucosa. There were no odontogenic signs, such as percussion and irregular pain against cold and hot stimulation in the affected teeth. Electronic pulp test revealed no devitalized teeth, with an increased response threshold of the teeth in the affected side versus the contralateral side. Laboratory tests showed lymphopenia of 1150/ μL (normal value: 1500–4000/ μL for adults) and 21.3% of total leucocyte count (5400/ μL). Hepatic and renal functions and serum levels of C-reactive protein and lactate dehydrogenase were within normal limits. Panoramic radiography showed minor dental caries in the lower right canine, 1st molar, and 1st premolar, but there were no abnormal radiolucent lesions in the mandible. A clinical diagnosis of mandibular ZSH was made. The patient discontinued lactation and was treated with valacyclovir (1000 mg/day) for 7 days. The mandibular pain and itching sensation in the preauricular and temporal regions peaked 2 days after the visit, but the symptoms markedly improved later. Serum examination of antibody levels against VZV-immunoglobulin M (VZV-IgM) upon initial consult was negative. The titer for VZV-IgG was 31.6 (normal value < 2.0). On follow-up after 3 weeks, the uncomfortable pain subsided and the sensation of the right side of the facial skin recovered. Hematologic testing showed improved lymphopenia, with a lymphocyte count of 1542/ μL (25.7% of total leucocyte count, 6000/ μL). The patient did not suffer from postherpetic neuralgia during 3 months follow-up.

In light of the increased prevalence of HZ during the pandemic, the present case serves as a reminder for considering atypical manifestations of HZ, such as ZSH, especially in post-COVID patients with lymphopenia. A Brazilian health system study found a 35% increase in the diagnosis of HZ during the pandemic compared with the same periods in prepandemic years [1]. A retrospective cohort study [11] demonstrated that COVID-19 patients over 50 years of age have a significantly higher risk of developing HZ, indicating that COVID-19 may provoke the reactivation of latent VZV.

A literature review of 29 patients with COVID-associated HZ reported that the onset of HZ rash ranged from 2 days before COVID-19 symptoms to 70 days after symptoms, at an average of 17 days [4]. A high proportion of trigeminal nerve involvement (12 out of 29 patients, 41%) has also been reported, but this does not agree with a previous report accounting for approximately 13%–22% [5,6], possibly indicating a higher risk of HZ involving the trigeminal nerve during the pandemic.

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Fig. 1. Clinical appearances

The left panel shows the lower face with slight swelling of the lower lip. The indolent rashes have involved across the chin midline for a few months. No zosteriform vesicles were observed. There was altered sensation in the right side of the lower lip, chin, and buccal skin, and slight upper cervical lymphadenopathy upon palpation of the affected side. The right panel shows intraoral appearance. The patient complained toothache of the right lower molars with an itching sensation on the ipsilateral side of the tongue and lower molar gingiva and with a reduced sensation of the buccal mucosa. The tiny abrasion of the intermaxillary commissure was accidentally injured by her fingernail tip when the patient persistently touched the mucosa to ascertain the localization of the uncomfortable area before the initial visit. The teeth in the affected side had an increased threshold in the electronic pulp test.

The etiological relationship between COVID-19 and the HZ remains to be fully elucidated. Both diseases are associated with lymphopenia, seen in over 70% of patients with COVID-19 [3] and 86.6% of COVID-associated HZ patients [4]. Suppressed cell-mediated immunity due to COVID-19 infection likely facilitates VZV reactivation. Furthermore, physical and emotional stress due to COVID-19 can also trigger reactivation.

In patients with ophthalmic ZSH before the pandemic, lymphocyte counts were lower than those of normal individuals, whereas there were no significant differences in age and serum VZV-IgG levels between the two groups [12]; Only 6.2% (4 out of 65 patients with ZSH) had VZV-IgG levels greater than 50, with a mean VZV-IgG value of 18 for all patients, which is similar to that of normal individuals in the control group. Serum VZV-IgG values can be considered unreliable to diagnose patients with persistent pain in the unilateral dermatomal distribution, though lymphocyte counts can be considered more helpful for the swift diagnosis of mandibular ZSH as well as ophthalmic ZSH.

Although the increasing reports of HZ during the COVID-19 pandemic [4,11] accordingly indicate that ZSH is a noteworthy and non-negligible disease, epidemic data and the mechanism on ZSH are still unavailable. Drago et al. [8] speculate that VZV in ZSH patients is mainly replicated by sensory ganglia and root of the cranial or spinal nerves, and that innate epidermal and mucosal immune response system and memory T cells depress the production of inflammatory cytokines, resulting in prevention of VZV spread in the skin and mucosa.

Considering the diagnostic difficulty of ZSH and the frequency of unknown originated neuropathic pain, the prevalence of orofacial ZSH may be underestimated. Given that ZSH patients experience significant pain and a higher prevalence of postherpetic neuralgia compared to HZ with shingles [8], its prompt diagnosis and appropriate management are challenging responsibilities for oral-maxillofacial specialists. Although ZSH can be confused with trigeminal neuralgia, the stabbing pain of trigeminal neuralgia lasts from a few seconds to several minutes triggered by touching the face or facial movements without altered sensation of the orofacial skin and mucosa. After excluding other causes such as malignant neoplasm or acute osteomyelitis, patients with anatomically localized intractable pain and altered sensation with ipsilateral distribution of an affected

trigeminal nerve, even those without rashes and herpetic eruptions on the face, should be managed in consideration of mandibular ZSH, especially during the COVID-19 pandemic.

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Consent

Patient's consent was obtained.

Declaration of Competing Interest

The authors declared no conflict of interest.

References

- [1] Maia CMF, Marques NP, de Lucena EHG, et al. Increased number of Herpes Zoster cases in Brazil related to the COVID-19 pandemic. *Int J Infect Dis* 2021;104:732–3.
- [2] Marra F, Parhar K, Huang B, Vadlamudi N. Risk factors for herpes zoster infection: a meta-analysis. *Open Forum Infect Dis* 2020;7:ofaa005.
- [3] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020;71:762–8.
- [4] Algaadi SA. Herpes zoster and COVID-19 infection: a coincidence or a causal relationship? *Infection* 2022;50:289–93.
- [5] Kaur R, Rani P, Malhotra D, Kaur R, Dass PK. A rare case report and appraisal of the literature on spontaneous tooth exfoliation associated with trigeminal herpes zoster. *Oral Maxillofac Surg* 2016;20:331–6.
- [6] Keskinruzgar A, Demirkol M, Ege B, Aras MH, Ay S. Rare involvement of herpes zoster in the mandibular branch of the trigeminal nerve: a case report and review of the literature. *Quintessence Int* 2015;46:163–70.
- [7] Chen N, Gordon R, Taylor M, Aung AK, Teh BM. An unusual distribution of herpes zoster mandibularis post total parotidectomy. *Int J Infect Dis* 2021;107:298–9.
- [8] Drago F, Herzum A, Ciccarese G, et al. Acute pain and postherpetic neuralgia related to Varicella zoster virus reactivation: comparison between typical herpes zoster and zoster sine herpette. *J Med Virol* 2019;91:287–95.
- [9] Zhou J, Li J, Ma L, Cao S. Zoster sine herpette: a review. *Korean J Pain* 2020;33:208–15.
- [10] Lee HY, Kim MG, Park DC, et al. Zoster sine herpette causing facial palsy. *Am J Otolaryngol* 2012;33:565–71.
- [11] Bhavsar A, Lonnet G, Wang C, et al. Increased risk of herpes zoster in adults >=50 years old diagnosed with COVID-19 in the United States. *Open Forum Infect Dis* 2022;9:ofac118.

- [12] Marumoto T, Hiratsuka Y, Murakami A. The significance of the determination of lymphocytes with clinical manifestation of ophthalmic zoster sine herpete. *Clin Ophthalmol* 2010;4:817–22.

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