



REVIEW

A narrative review and clinical anatomy of herpes zoster infection following COVID-19 vaccination

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Abstract

Introduction: In this review, cases of herpes zoster (HZ) infection following receipt of COVID-19 vaccines will be analyzed. We also present two cases of oral HZ following the COVID-19 vaccine and discuss this clinical anatomy.

Materials and Methods: A database search using PubMed was conducted in August 2021 and 20 articles were found to be eligible for review. Patient data and vaccine information were analyzed. In addition, two cases of oral HZ infection following the receipt of COVID-19 vaccines are presented.

Results: A total of 399 cases were identified. The affected dermatomes mimicked the regular distribution of HZ. For the dermatomes of the face, the various reports used different ways to describe the areas involved; CNV, CNV1, CNV2, CNV3, lower jaw, forehead, and under the eyebrow (CNV, 2 cases; CNV1, 4 cases; CNV2, 3 cases; and CNV3, 3 cases). Some patients who had a history of varicella zoster virus vaccination had HZ following the COVID-19 vaccination. Two patients with oral HZ following vaccination were found to have involvement of the greater palatine nerve.

Conclusions: Vaccine-related HZ cases have been reported worldwide. Although many studies with a larger number of cases are ongoing, detailed information can be obtained from case reviews as reported herein.

KEYWORDS

clinical anatomy, complications, COVID-19, infection, oral herpes zoster, palate, pandemic, reactivation, vaccination, varicella zoster virus

1 | INTRODUCTION

The Food and Drug Administration issued Emergency Use Authorizations for Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273)

COVID-19 vaccines in December 2020 (McMahon et al., 2021). Since then, several types of vaccines have been used worldwide. The adverse events associated with the vaccinations include anemia, skin reactions, and lymphopenia although the cause of many of these

adverse effects is still unclear (Barda et al., 2021). In many countries, nationwide studies are ongoing and data from some of these are currently being analyzed (Català et al., 2021; Barda et al., 2021; Coronavirus Vaccine—Weekly Summary of Yellow Card Reporting. Updated 25 March, 2021. Available online: Website: <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>, accessed on September 7, 2021).

Recently, cases of herpes zoster (HZ) characterized by reactivation of varicella zoster virus (VZV) following COVID-19 vaccines have been reported in the literature (Barda et al., 2021; Psychogiou et al., 2021; Rodríguez-Jiménez et al., 2021). It is believed that VZV is latent in the spinal dorsal root ganglia (DRG) and trigeminal ganglia (TG). In cases of reactivation of the VZV in the DRG, HZ will appear in the corresponding dermatome of the sensory nerve originating from the DRG (Gagliardi et al., 2016; Psychogiou et al., 2021). The reactivation of the VZV in the TG causes HZ reactivation in the upper, middle, lower face, or oral cavity depending on involvement of V1, V2, or V3 divisions of the trigeminal nerve.

Studies have shown that vaccines such as for hepatitis A, influenza, rabies, and Japanese encephalitis can trigger the reactivation of the HZ (Eid et al., 2021; Vastarella et al., 2021; Wollina et al., 2020; Wollina et al., 2021). Although the prognosis is predictable, the etiology and association with vaccines and VZV reactivation is still unclear.

In this review, HZ cases following COVID-19 vaccinations will be analyzed to better illustrate the involvement from different countries.

We also present two cases of oral HZ following COVID-19 vaccination.

2 | MATERIALS AND METHODS

2.1 | Database search

A database search using PubMed was conducted in August 2021. The following keywords were used in the search: “((herpes zoster) AND (covid-19)) AND (vaccine)” or “((herpes zoster) AND (covid-19)) AND (vaccination)”. Thirty-eight articles were identified. The first author reviewed the titles and abstracts of the results and excluded studies that were duplicated or not written in English. A total of 22 studies underwent full-text assessment. Finally, 20 studies describing HZ after COVID-19 vaccination were included noting the publication year, first author, country, journal, and the number of cases included in the article (Table 1).

2.2 | Data analysis

A total number of reported cases of herpes zoster after COVID-19 vaccination was calculated based on the data found in 20 articles. The age, sex, vaccine type, dose that triggered the HZ reactivation (first or second), duration from the vaccination until the skin reaction appeared (days), and affected dermatome were noted.

In addition, two case illustrations of HZ following COVID-19 vaccination in the oral cavity will be presented.

	Year	First author	Country	Journal	No. of cases
1	2021	Rodríguez-Jiménez	Spain	JAAD Case Rep	5
2	2021	Özdemir	Turkey	J Eur Acad Dermatol Venereol	2
3	2021	Aksu	Turkey	Clin Exp Vaccine Res	1
4	2021	Català	Spain	Br J Dermatol	41
5	2021	Lee	USA	J Cosmet Dermatol	20
6	2021	Alpalhão	Portugal	J Eur Acad Dermatol Venereol	4
7	2021	Barda	Israel	N Engl J Med	283
8	2021	Psychogiou	Greece	Vaccines (Basel)	7
9	2021	Channa	USA	JAAD Case Rep	1
10	2021	Arora	India	J Cosmet Dermatol	1
11	2021	Vastarella	Italy	J Eur Acad Dermatol Venereol	3
12	2021	Tessas	Finland	J Eur Acad Dermatol Venereol	1
13	2021	Eid	Lebanon	J Med Virol	1
14	2021	Chiu	Taiwan	QJM	3
15	2021	Bostan	Turkey	J Cosmet Dermatol	1
16	2021	Furer	Israel	Ann Rheum Dis	6
17	2021	McMahon	Multinations	J Am Acad Dermatol	10
18	2021	Furer	Israel	Rheumatology (Oxford)	6
19	2021	van Dam	Netherlands	Int J Infect Dis	2
20	2021	David	USA	J Drugs Dermatol	1

TABLE 1 The publication year, first author, country, journal, and the number of cases included in the article

3 | RESULTS

Twenty articles published in 2021 were analyzed. A total of 399 cases were reported from 20 articles. The affected patients' sex, mean age, and age range are shown in Table 2. The vaccine type, the dose that triggered the HZ reactivation (first or second), and the duration from the vaccination to skin reaction are shown in Table 3. BNT162b2 (Pfizer) is the most reported type of vaccine (351/399). The study by Barda et al. (2021) which had the largest number of HZ cases in this review used BNT162b2 vaccine ($n = 283$). HZ after inactivated COVID-19 vaccination was reported only in reports from India and Turkey.

3.1 | Affected dermatome

The dermatomes affected were cranial nerve V in 12 cases, the cervical region in 11 cases, the thoracic region in 24 cases, and the lumbar/sacral regions in seven cases. When multiple regions were affected in one patient, it was counted as multiple cases. For the dermatomes of the face, the various reports used different ways to describe the areas involved; CNV, CNV1, CNV2, CNV3, lower jaw, forehead, and under the eyebrow (CNV, two cases; CNV1, four cases; CNV2, three cases; CNV3, three cases). To our knowledge, no previous reports have described HZ involvement of the CN V dermatome in the oral cavity.

3.2 | Prior history of herpes zoster or varicella

A total of 24 patients from seven articles mentioned a prior history of HZ or varicella and 16 patients had a prior history of these (Alpalhão & Filipe, 2021; Channa et al., 2021; Furer, Eviatar, et al., 2021; Lee et al., 2021; Psychogiou et al., 2021; Tensas & Kluger, 2021; van Dam et al., 2021).

3.3 | History of the varicella zoster virus vaccination

A total of 20 patients in four articles mentioned a history of a VZV vaccination and five patients had received a VZV vaccination before the COVID-19 vaccine (Channa et al., 2021; Furer, Zisman, et al., 2021; Lee et al., 2021; Psychogiou et al., 2021). Four out of the

five patients received the VZV vaccine in 2019 or 2020 (Channa et al., 2021; Furer, Zisman, et al., 2021; Lee et al., 2021).

3.4 | Other medical history of the patients

The medical history of the patients who developed HZ after COVID-19 vaccination varied and included the following: type II diabetes mellitus, hypertension, coronary artery disease, dysrhythmia, dyslipidemia, cerebrovascular accident, chronic pulmonary obstructive disease, anxiety, and antineutrophilic cytoplasmic antibody-related glomerulonephritis.

3.5 | Treatment

Treatments described in the literature were the same as for patients in the general population with HZ.

3.6 | Two cases of herpes zoster in the oral cavity following COVID-19 vaccination

3.6.1 | Case 1

A 75-year-old Japanese female visited the authors' (H.F. and N.F.) general dental practice for multiple unilateral small ulcers on the left hard palate. The patient had a medical history of hypertension and received a second dose of BNT162b2 vaccine 11 days before her symptoms began. Based on the clinical findings, the patient was diagnosed with oral HZ (Figure 1). There were no other symptoms in the oral cavity or other skin reaction involvement of the CN V dermatomes or other spinal nerves. The symptom disappeared in a week without treatment.

3.6.2 | Case 2

A 77-year-old Japanese female visited the authors' (H.F. and N. F.) general dental practice for multiple unilateral ulcers on the left hard palate. The patient had a history of hypertension and chronic kidney disease requiring dialysis. She received the second dose of BNT162b2 vaccine 38 days before the symptoms began. The patient was

TABLE 2 Patients' sex, mean age, and age range

	No. of cases for analysis		No. of articles cited for analysis and first author of the article not cited for analysis (out of 20 articles in Table 1)				
Sex	399	Female	54	17	None		
		Male	46				
		Unknown	299	3			
Mean age	100		58.9	17	Barda	Furer	McMahon
Age range	59		21–94	16	Barda	Furer	McMahon Català

TABLE 3 The vaccine type, the dose that triggered the HZ reactivation, and the duration from the vaccination to skin reaction

	No. of cases for analysis			No. of articles cited for analysis and the first author of the article not cited for analysis (out of 20 articles in Table 1)				
Vaccine type	399	BNT162b2(Pfizer)	351	20	None			
		mRNA-1273 (Moderna)	28					
		AZD1222 (AstraZeneca)	14					
		mRNA COVID vaccine (not specified)	1					
		inactivated SARS-CoV-2 vaccine	5					
The dose reactivating HV	399	First dose	77	20	None			
		Second dose	32					
		Unknown (or needed only one shot)	290					
Duration (days)	59	Minimum	1	16	Barda	Furer	McMahon	Català
		Maximum	24					
		Mean	6.75					

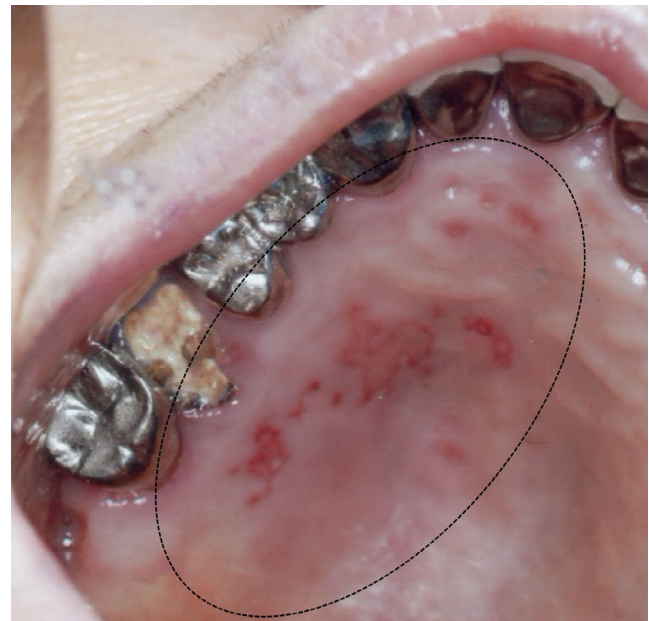
**FIGURE 1** A mirror image of the multiple unilateral small ulcers on the left hard palate (dotted circle). The lesions are limited to the molar and premolar areas

diagnosed with oral HZ based on her clinical findings (Figure 2). There were no other symptoms in the oral cavity and no other skin involvement in the CN V dermatome or other spinal nerve dermatomes. The patient was treated with amenamevir 200 mg for a week and ulcers disappeared.

4 | DISCUSSION

4.1 | Etiology

The EudraVigilance, European database of suspected adverse drug reaction reports, reported 4103 HZ cases, 590 HZ cases, and 2143 HZ cases following BNT162b2, mRNA-1273 and AZD1222,

**FIGURE 2** A mirror image of the multiple unilateral ulcers on the left hard palate (dotted circle). The lesions extend to the molar, premolar, canine, and incisor areas

respectively (Website: <http://www.adrreports.eu/>. Accessed on July 27, 2021; van Dam et al., 2021). In an Israeli study, Barda et al. (2021) reviewed 888,647 cases and found that 283 cases (0.03%) had HZ after BNT162b2 COVID-19 vaccination. Furer, Zisman, et al. (2021) reported 6 cases of HZ (1.2%) following BNT162b2 COVID-19 vaccination in 491 patients with autoimmune inflammatory rheumatic diseases and found none (0%) in a control group ($n = 99$).

In this review, we found that the reactivation of VZV following the COVID-19 vaccines has been reported all over the world and with different types of vaccines. Reactivation of VZV following the vaccination using inactivated COVID-19 has only been reported in India

and Turkey (Aksu & Öztürk, 2021; Arora et al., 2021; Bostan & Yalici-Armagan, 2021; Özdemir et al., 2021). The affected age had a wide range (21–94 year old) with a mean of 58.9 years. Reactivation of VZV after the first dose of vaccine seems more common than the second dose although we were unable to perform statistical analyses of this. Duration from the vaccination to skin reaction ranged from 1 to 24 days with a mean of 6.75 days. This result is similar to the case series findings of 7.6 days (three cases) reported by Vastarella et al. (2021) and 5.4 days (5 cases) reported by Rodríguez-Jiménez et al. (2021). The median time from hospitalization after COVID-19 infection to HZ appearing was 5.5 days (Tartari et al., 2020). Although the mechanism of vaccine-induced HZ is still unclear some suggested vaccines might cause immunomodulation and lead to herpes virus reactivation (Özdemir et al., 2021; Walter et al., 1999).

Our review found that most of the literature involves case reports/series without control groups. It was not clear that the incidence of HZ following the COVID-19 vaccine was higher than the incidence of HZ in the general population. One study by Barda et al. (2021) included 283 cases of HZ (70.9% of all cases in this review) after vaccination and 204 cases of HZ in a control group.

4.2 | Clinical anatomy of the dermatome

HZ can be one of the causes of facial nerve palsy after vaccination (Peitersen, 2002; Coronavirus Vaccine—Weekly Summary of Yellow Card Reporting. Updated 25 March 2021. Available online: Website: <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>, accessed on September 7, 2021). The trigeminal ganglion is considered the location of the latent VZV. Ramsay-Hunt syndrome, facial nerve palsy with other symptoms such as ear pain and vesicles in the ear, is caused by infection of the reactivated VZV of the

geniculate ganglion of the facial nerve (Volpi, 2007). However, there is still no consensus of how the VZV reaches the facial and other cranial nerves.

Based on our review, any dermatome of cranial nerve V and spinal nerves can be affected by HZ following COVID-19 vaccination, which mimics the regular HZ. Oral findings of HZ are well known (Santosh & Muddana, 2020). However, our literature review did not find any cases of VZV reactivation in the oral cavity following COVID-19 vaccination. Therefore, the two case illustrations presented herein are unique. Although a large national database in the UK based on the spontaneous reports listed many oral lesions including oral herpes, it did not report cases of oral HZ (Coronavirus Vaccine—Weekly Summary of Yellow Card Reporting. Updated March 25, 2021. Available online: Website: <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>, accessed on September 7, 2021).

Interestingly, our two case illustrations had involvement of only the hard palate in the distribution of V2 (greater palatine nerve) (Figure 3). Other V2 dermatome regions of V2 for example, midface and nasal septum, were not affected.

4.3 | Vaccine-related reactivation

Brosh-Nissimov et al. (2021) compared oropharyngeal reactivation of herpes viruses before and 1 week after BNT162b2 vaccination and concluded that they did not find any evidence of increased oropharyngeal reactivation 1 week after BNT162b2 vaccination, but not specifically VZV. There is also no definition of vaccine-related reactivation in terms of duration. In the study by Brosh-Nissimov et al. (2021), “1 week” was used to determine the vaccine-related virus reactivation. Català et al. (2021) included patients with cutaneous reactions within 21 days after any dose of vaccine. However, our review revealed that the latent period of vaccine-related HZ is from

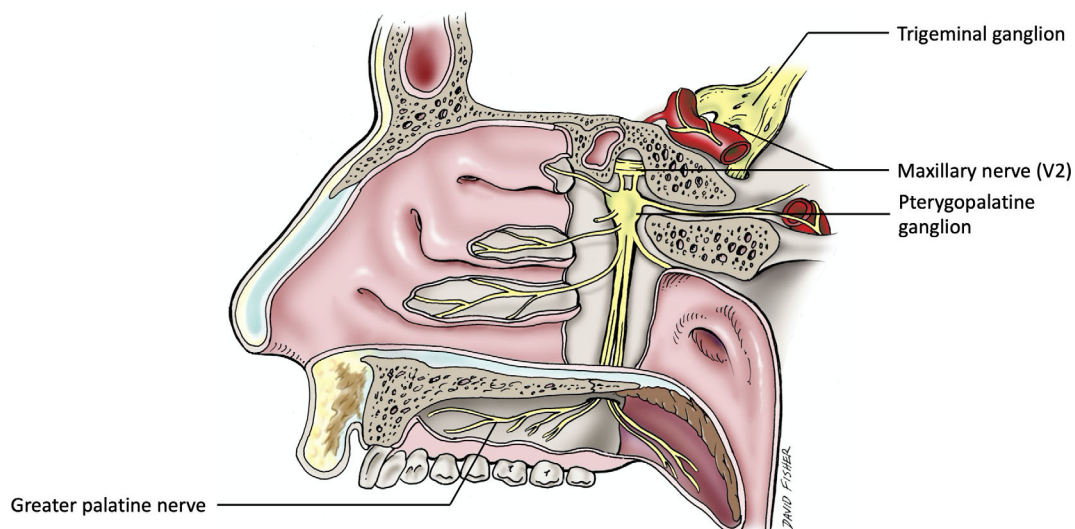


FIGURE 3 A schematic drawing of the greater palatine nerve arising from the maxillary nerve

1 to 24 days after vaccination. Additionally, our Case 2 became symptomatic 38 days after vaccination. Therefore, it is difficult to determine if this was vaccine-related or not.

5 | CONCLUSIONS

Vaccine-related HZ cases have been reported worldwide. Although many national studies with larger number of cases are ongoing, detailed patient information can be obtained from individual case reports/series. As we identified two patients with oral HZ in a short period following COVID-19 vaccination, other cases might be missed or misdiagnosed just a stomatitis or oral herpes. Dentists, dermatologists, and otolaryngologists should be aware that the patients who have received COVID-19 vaccinations might present with pain in the oral cavity and oropharynx due to VZV reactivation. The dermatome in the oral cavity is often forgotten as it is not as easily seen on physical examination. Moreover, this region might be better described as an “epidermatome” or “mucotome.”

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