A Comparison of SARS-CoV-2 Infection-related and COVID-19 Vaccine-related Herpes Zoster; A Narrative Review

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Abstract

The are many cases of coincidence of herpes zoster in pre-COVID-19 infection or post-COVID-19 vaccination period and some expert or specialist experiences about increased prevalence of zona in the COVID-19 era that highlights the probability of SARS-CoV-2 infection and vaccine associated immune dysregulation that reactivates latent varicella zoster virus (VZV) infection. In this comprehensive comparative review we have discussed the various aspects of COVID-19 pandemic-related zona as the peri-COVID or post-vaccine zoster which is considered as one of the most prevalent dermatological adverse reactions in such circumstances and should be diagnosed and managed in the best possible way. By a comparative approach there are many similarities and differences regarding herpes zoster in theses 2 certain conditions.

Key words: COVID-19, SARS-CoV-2, Varicella Zoster Virus, Zoster, Zona, COVID-19 Vaccine, Vaccination, Virus Reactivation, Comparative, Review.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) has revealed a great range of strange associations between the novel virus and many phenomena. Herpes zoster incidence has increased considerably since the beginning of the severe acute respiratory disease coronavirus 2 (SARS-CoV-2) infection pandemic (1). Many cases have been demonstrated following de novo SARS-CoV-2 infection, while others have been reported after SARS-CoV-2 vaccination (2, 3). Reactivation of herpes zoster virus has always been known to be due to aging or immunosuppression. However, its occurrence after SARS-CoV-2 infection raises important questions about the immunosuppressing properties of this virus. Moreover, its high incidence following COVID-19 vaccination, more than any other vaccines, is also an issue of discussion. Dermatologic manifestations of SARS-CoV-2 range from a simple urticarial rash to life-threatening complications like vasculitis or Stevens–Johnson syndrome (4, 5). Vesicular eruptions consist a group of COVID-related cutaneous manifestations which are usually diffuse so as known as varicella-like eruptions (6). However, this condition can be as a sign of zoster. “Shingles” or “herpes zoster” commonly occurs in immunocompromised or older individuals. However, the COVID-19 pandemic has brought about several zoster cases appearing in immunocompetent individuals (7, 8). On the other hand, zoster reactivation has been one of the most common adverse events of many vaccines, including...
SARS-CoV-2 vaccines(9).

While many consider this phenomenon as a mere coincidence, the increased prevalence in the COVID era should be considered a threat as SARS-CoV-2 infection and vaccine associated immune dysregulation can reactivate latent VZV infection(10).

Here, we have discussed various aspects of COVID-19 pandemic-associated zoster with an overview of the literature.

METHODS

For writing this review we searched the evidence based on the databases PubMed (http://ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Science Direct (https://www.sciencedirect.com), and Google Scholar (https://scholar.google.com/) and our key words were COVID-19, SARS-CoV-2, Varicella zoster virus, VZV, Zoster, Zona, COVID-19 vaccine and Vaccination.

RESULTS AND DISCUSSION

Definition

Varicella zoster virus (VZV) is a neurotropic herpes virus that becomes dormant in neural ganglions after being manifested as varicella (chickenpox). Reactivation of the virus through the life of an individual with a history of chickenpox, is termed as shingles or zoster(11). Older age, immunosuppression, trauma, infections, vaccination and stress are predisposing factors of zoster reactivation(12). However, the onset of zoster after SARS-CoV-2 infection and vaccination is the issue of our discussion.

Pathophysiology

The decreased number of natural killer cells and absolute lymphocytes, particularly CD3+ CD8+ T cells, in the settings of SARS-CoV-2 infection may account for VZV reactivation(13, 14). This condition is more common in severe cases of COVID-19, in which profound decrease in T lymphocytes leads to an immunosuppressive state(15). However, the immune system the dysregulation imposed by the physical and mental stress might be the underlying mechanism for zoster reactivation in mild SARS-CoV-2 infections(16).

On the other hand, zoster reactivation following any vaccines, including SARS-CoV-2 vaccines, seems to be the result of immune system stimulation which induces a cellular response. This event is more prominent for CD8+ and T helper type 1 CD4+ T cells(17). This is in contrast with the decreased number of CD8+ lymphocyte count which is the trigger for zoster reactivation in the settings of SARS-CoV-2 infection. This paradox is explained if we suppose that COVID vaccination leads to massive shift of naïve CD8+ cells, which prevents VZV-specific CD8+ cells from controlling VZV(18). However, many authorities believe that the immunomodulation due to a dose dependent and transient lymphocytopenia occurring shortly after SARS-CoV-2 vaccination is the pathophysiologic mechanism for herpes zoster reactivation from latency, similar to COVID-related zoster(19, 20). Moreover, it is hypothesized that interferon responses are changed after vaccination, which is a trigger for developing zoster(21).

Epidemiology and risk factors

In general the mean age of onset is over 60 years of age for herpes zoster reactivation, unless in immunocompromised individuals like cancer and rheumatologic patients(22). However, zoster following both SARS-CoV-2 infection and SARS-CoV-2 vaccination has been demonstrated in younger ages(23, 24).

The iatrogenic immunosuppression imposed by the SARS-CoV-2 infection, due to the increased prevalence of corticosteroid use, is the main underlying reason for zoster activation in severe cases of SARS-CoV-2 infection. However, COVID-19 per se induces an immunosuppressed state, especially in severe and critical cases(13). Moreover, the occurrence in less severe COVID-19 cases could be the result of physical and psychological stress imposed by the illness(13, 25).

Vaccines, including SARS-CoV-2 vaccines, have accounted for a great number of zoster reactivations recently. However, most COVID vaccine-related shingles have occurred in individuals with an underlying immunorheumatologic disorder like rheumatoid arthritis or those on immunosuppressive agents(26, 27). Most cases of COVID vaccine-related zosteres have been reported with mRNA vaccines. Furthermore, zoster reactivation have occurred more commonly following the first dose of SARS-CoV-2 vaccine, compared with the second dose(23).

Manifestations

Most cases of SARS-CoV-2 related zosteres have occurred in less than 10 days after infection(10). Some even happened concurrently with SARS-CoV-2 infection onset. Nevertheless, zoster onset might be a sign of latent SARS-CoV-2 infection, appearing in the settings of a subclinical COVID-19(28). However, there have been cases of zoster which activated several weeks after SARS-CoV-2 recovery(2, 29). The clinical manifestation of zoster usually include painful, unilateral vesicular lesions in dermatomal distribution. This condition is usually preceded by an itching or stinging(30). The post-COVID zosteres usually have similar characteristics of those unrelated to SARS-CoV-2 infection However, they may present with atypical or severe manifestations, such as necrotic or haemorrhagic herpetic eruptions, multi-dermatomal or disseminated lesions, trigeminal dermatome involvement or accompaniment of severe neuralgia, all related to impaired immunity(25, 31-33). Children have also been victims of rare types of zoster like herpes zoster ophthalmicus after being infected with SARS-CoV-2.
CoV-2 infection(24).
Most cases of vaccine-related herpes zoster have occurred within one week after vaccination; some even have occurred concurrently with COVID vaccination(10). However, the latent period has been reported to be up to one month following COVID-19 vaccination(23, 34). In addition, recurrent herpes zoster has also been reported following COVID vaccination in an immunosuppressed patient(35). The COVID-vaccine related zosters also can present atypically. There have been COVID vaccine-associated atypical zosters arising in in the oral cavity and hard palate without skin involvement(23, 36). Moreover, severe zoster cases complicated with small vessel vasculitis, meningitis or acute retinal necrosis have also been reported following COVID vaccination(37-39).

Diagnosis
The diagnosis of zoster is usually straightforward. However, it is recommended to confirm the diagnosis by Tzanck smear or PCR test, especially in those cases presenting with atypical manifestations(40). However, the more important issue is to exclude a subclinical SARS-CoV-2 infection in any patient presenting with herpes zoster reactivation during the COVID-19 pandemic as these patients can unintentionally spread the SARS-CoV-2 infection to others(28).

Differential diagnosis
The unexpected onset of zoster after COVID-19 infection or vaccination, and also its atypical presentations can lead to a significant delay in the diagnosis. For example, there have been post-COVID zoster cases which presented with purpuric eruptions mimicking vasculitis or drug reactions and arose diagnostic challenges(32). Other interesting diagnostic challenges included a post-COVID vaccine zoster which was misdiagnosed as “COVID Arm” or a simple stomatitis or oral herpes(36, 41).

Treatment
Antiviral agents, including acyclovir, valacyclovir and famciclovir, are the common therapeutics used for zoster activation in any situation. The decision to administer the medications intravenously depends upon the severity of the illness and the patient’s immune status(42). The important point is the necessity to timely initiate therapy, since treatment is sometimes delayed due to the atypical presentations that mislead the practitioner and the patient.

Prevention
Boosting cell-mediated immunity through zoster vaccination, especially in the elderly can prevent VZV reactivation following SARS-CoV-2 infection or vaccination. This can prevent further zoster-related complications and morbidity, especially in cases involving the trigeminal nerve(43). Moreover, some authorities recommend prophylactic antiviral agents such as oral valacyclovir for high-risk individuals who intend to be vaccinated against SARS-CoV-2 and are likely to develop zoster following vaccination(26).

Prognosis
Most cases of zoster, either following SARS-CoV-2 infection or vaccination, have favorable outcome; however, disseminated cases and those with atypical presentations or ophthalmic nerve involvement might lead to severe or lethal complications(32).

Recommendations
There are many studies focusing on cytokine storm and immune-disturbance during COVID-19 infection or post-COVID-19 vaccination which results in many mucocutaneous adverse reactions that should be kept in mind for better diagnosis and treatment of these side effects and also use available data for probable prognosis of observed complication, so far, zona is not an exception (44-53).

CONCLUSION
Various dermatologic manifestations of SARS-CoV-2 infection and post-COVID cutaneous adverse events are continually emerging, some with a strong association, and some being only a coincidence. Further studies are needed to establish the causal relationship. However, despite the uncertainty about the relationship between SARS-CoV-2 infection and vaccination and zoster, every clinician, particularly dermatologist, should be aware of the increasing rate of herpes zoster reactivation in the COVID era in order not to delay the diagnosis and timely initiate therapy and prevent complications.

ETHICAL CONSIDERATION
Not Applicable.

DECLARATION OF CONFLICTING INTERESTS
None to declare.

DATA AVAILABILITY
Not Applicable.

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AUTHOR CONTRIBUTIONS
ZMA, ZA, AG contributed to the study idea and design, ZMA, ZA, PH, AJ and AG conducted database search, literature review, and drafting and editing the final version.
AG contributed to the supervision of the study and submitting the paper. All authors contributed to drafting the manuscript and revising the manuscript critically for importance intellectual content and read and approved the final version to be published and agreed to be accountable for all aspects of the work. All authors agreed on the order in which their names are listed in the manuscript.

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