Varicella-Zoster Virus Reactivation amid the COVID-19 pandemic- Do we need to be vigilant? A mini review

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Abstract
Reactivation of varicella-zoster infection has been noted in a subset of COVID-19 patients. This has been attributed to immune dysregulation resulting from SARS-CoV-2 infection. Majority individuals presented with shingles, however, neurological complications such as meningoencephalitis and acute retinal necrosis were also reported. Diagnosis in most cases was made on clinical grounds, however, for complications such as meningoencephalitis, the standard investigative measures such as polymerase chain reaction tests (PCR) were conducted. Post-herpetic neuralgia (PHN), a less common sequel of shingles, was witnessed despite the early administration of therapy. Most cases were resolved with antiviral therapy; however, in some instances, corticosteroids had to be administered.

Key words: herpes zoster, COVID-19, acyclovir, ganciclovir

Introduction
SARS-CoV2, the causative agent of the COVID-19 pandemic, is a member of the Coronoviridae family which includes single-stranded RNA viruses. Similar strains such as SARS-COV and MERS-COV have also been involved in major outbreaks and are evidenced to demonstrate widespread systemic damage. The virus is associated with mortality rates between 3-4% and imposes a greater risk of morbid outcomes in the elderly, immunocompromised individuals, and those with underlying risk factors such as obesity, diabetes, and hypertension [1].

This virus presents with a cluster of heterogeneous symptoms involving the respiratory, gastrointestinal, and nervous systems [2,3,4]. Skin involvement in COVID-19 is also hypothesized to occur. This may be due to direct immune damage by SARS-COV2, or indirectly as a manifestation of systemic involvement [5,6]. Skin symptoms range from widespread erythema, urticaria, and varicella-like rash in a subset of individuals. Some asymptomatic individuals have demonstrated similar findings before the development of the typical COVID-19 presentation [7-10]. However, the reactivation of the Varicella-Zoster virus (VZV) is a peculiar finding. The causative agent, Varicella-Zoster Virus (VZV), latently infects the sensory ganglia after the primary exanthem of Chickenpox, usually acquired in childhood. This virus has the propensity to reactivate and cause an excruciatingly painful vesicular eruption along the affected dermatome, which may even precipitate the debilitating sequelae of post-herpetic neuralgia [11].

We, hereby, present a brief review of the occurrences of VZV reactivation in COVID-19 patients.

Pathogenesis
SARS-COV2 results in a hyperinflammatory state [12] and the subsequent immune dysregulation is postulated to be the potential cause of reactivation. The reactivation is attributed to the immune dysregulation resulting from hyperinflammatory states due to SARS COV-2. Earlier accounts of leukopenia and lymphopenia in COVID-19 patients [13] propose that a reduction in lymphocytes, predominantly CD3 and CD8 cells, may have given rise to the reactivation [14]. Additionally, a low lymphocyte count predisposes the elderly population to an eruption [15]. Moreover, Li et al. stated that a lower CD4 count or derangement in cellular function appears to result in a more dismal prognosis (Figure 1) [16].
Clinical features and epidemiology

Case reports around the globe have reported the reactivation of herpes zoster in patients with evidence of COVID-19, with or without the typical respiratory symptoms. Although considered to be a disease of old [17] and immunosuppressed individuals, the younger immunocompetent people were not entirely spared from the infection in the setting of COVID-19 [18]. The number of reports was not sufficient to establish a gender predilection nor could they assess any association between comorbidities and the virus' reactivation. Nevertheless, some patients had a positive history of hypertension [18-20]. The diagnoses were made clinically except in a few where VZV serology was performed [21]. Some were asymptomatic for COVID-19, while in others the eruptions followed, with varying time intervals between the COVID-19 symptoms and reactivation, across the studies.

In a case series from Italy, four critically ill elderly patients developed herpes zoster, three of which had necrotic lesions. Intriguingly, one of the patients who was on immunosuppressive drugs due to a cardiac transplant had the least complicated clinical picture. This contrasts with the fact that immunosuppression is held as a risk factor for reactivation. However, all four patients had lymphopenia, especially decreased CD8+ and CD3+ cells, which might have contributed to the cessation of latency [22]. Lymphopenia was also observed in a 58-year-old male from Massachusetts, who developed meningitis in addition to shingles. He complained of severe headaches and abdominal symptoms before the development of a rash. Typical chest symptoms and meningitis followed several days later [23].

Elsaie et al. mentioned another such case in which respiratory symptoms of COVID-19 and ground-glass opacities on the computed tomography (CT) scan appeared two days after the development of vesicles. This patient was a 68-year-old hypertensive male whose rash later turned hemorrhagic. Another case was that of a 60-year-old hypertensive female who had been experiencing dyspnea for five days before the onset of rash, but this was interpreted as a seasonal allergy by her attendants. She was tested positive for COVID-19 a week before. The rash later turned hemorrhagic. This prompts the clinicians to explore the risk factors and look into alternative drug regimens. Patel accounted for encephalitis in an 83-year-old individual with coexisting comorbidities who have been diagnosed with COVID-19 a week before. The characteristic involvement of the medial temporal lobe on the left side on magnetic resonance imaging (MRI) was followed by confirmation on the cerebrospinal fluid analysis (CSF) analysis. Immunosuppression was speculated to be the cause, although, there was no history of corticosteroids use. Subarachnoid hemorrhage secondary to an aneurysm and spinal cord infarcts were additionally reported, both attributed to the deranged clotting mechanism resulting from either VZV or SARS-CoV-2, or both [31].

Hassanpour reported a case of acute retinal necrosis in a COVID-19 patient following an episode of meningococcal disease caused by reactivation of VZV. The diagnosis was initially made on radiological investigations with CSF PCR negative for the strain; however, the PCR analysis of the aqueous humor later turned out to be positive [32].

Severity of the lesions/ complications

Reactivation lesions displayed varying degrees of severity and post-herpetic neuralgia was observed in two of them [21,25], although elderly and immunocompromised populations are more vulnerable to developing PHN [27,28,29]. Wei et al. hypothesized that lower CD8 T-cell lymphocytes in old individuals might have an association with the development of PHN, whereas the actual mechanism is not known [15]. Immunosuppressed and those with HIV are at a higher risk of developing the necrotic zoster type. However, the incidence of this type in healthy individuals indicates the decrement of immune cells, B and T-lymphocytes, and Natural Killer cells by COVID-19 [30]. Shors et al. demonstrated that timely initiation of antiviral therapy could not prevent the incidence of PHN [25]. This prompts the clinicians to explore the risk factors and look into alternative drug regimens. Patel accounted for encephalitis in an 83-year-old individual with coexisting comorbidities who have been diagnosed with COVID-19 a week before. The characteristic involvement of the medial temporal lobe on the left side on magnetic resonance imaging (MRI) was followed by confirmation on the cerebrospinal fluid analysis (CSF) analysis. Immunosuppression was speculated to be the cause, although, there was no history of corticosteroids use. Subarachnoid hemorrhage secondary to an aneurysm and spinal cord infarcts were additionally reported, both attributed to the deranged clotting mechanism resulting from either VZV or SARS-CoV-2, or both [31].

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Treatment and prognosis

In most cases, the symptoms resolved with antivirals such as acyclovir/valacyclovir/feraciclovir. The pain and fever subsided on taking analgesics and anti-inflammatory medications—acetaminophen, tramadol, and gabapentin.
but also avert the risk of mini-outbreaks of Chickenpox, which were also prescribed. Pona et al. used no antiviral therapy, and gabapentin was only administered to relieve the pain [20]. The neurological complications resulting from VZV were treated with intravenous acyclovir and ganciclovir [31,32].

**Conclusion**

Such atypical presentations necessitate prompt clinical suspicion. Adequate isolation protocol is mandated in these patients. This will not only prevent transmission of COVID-19 but also avert the risk of mini-outbreaks of Chickenpox, which may further add to the current healthcare burden. We call upon the scientific committee to pour their insight into the matter and devise recommendations for Herpes Zoster vaccination in situations such as the given SARS CoV-2 pandemic. Although research is lacking, given the contagiousness of the VZV, we also recommend vaccination of family members and close contacts of such patients, especially in the pediatric age group.

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