Infection (2022) 50:289–293
https://doi.org/10.1007/s15010-021-01714-6

REVIEW

Herpes zoster and COVID-19 infection: a coincidence or a causal relationship?

Salim Ali Algaadi[1]

Received: 22 July 2021 / Accepted: 5 October 2021 / Published online: 22 November 2021

Abstract

The first cases of COVID-19 were reported in Wuhan, China, in December 2019. Skin manifestations of COVID-19 vary, among which herpes zoster has recently been found to be associated with the infection. We studied the available literature regarding COVID-19-associated herpes zoster (HZ). We searched the PubMed and Scopus databases for available literature till 20th of May 2021 using the following terms: 'Herpes zoster' or 'Varicella zoster virus' and "COVID-19" or "coronavirus disease" or "SARS-CoV-2". This search revealed 87 publications, of which 29 articles met the inclusion criteria. A total of 29 patients had HZ associated with COVID-19 infection. The patients' ages ranged from 7 to 82 years, averaging 56 years. Thirteen patients (45%) were men and 16 (55%) women. We summarized the demographic data, clinical data, comorbidities, treatment used, lymphocyte count, and distribution and timeline of HZ rash in COVID patients. Lymphopenia was prevalent in 86.6% of patients (where lymphocyte data were available). We discuss possible causes of HZ due to COVID-19. More and larger studies are needed to confirm any relationship between these two infections; however, this study may pave the way for similar studies on this topic.

Keywords COVID-19 · Herpes zoster · Lymphopenia · Varicilla zoster virus

Introduction

The first cases of COVID-19 were reported in Wuhan, China, in December 2019 [1] and it has spread widely and rapidly across the world and was declared a pandemic in March 2020 [2].

Cutaneous manifestations associated with COVID-19 are heterogeneous and can be classified into six main patterns: maculopapular rash, urticarial pattern, chilblain-like acral pattern, vesicular lesions, livedo reticularis-livedo racemosa-like pattern, and purpuric "vasculitic" pattern [3].

HZ is a reactivation of varicella-zoster virus (VZV) primary infection (chickenpox). Reactivation of dormant VZV infection can be caused by older age, immunosuppression, mechanical trauma, and recent psychological stress [4]. HZ cases have increased during the COVID-19 pandemic, which may be attributed to lymphopenia resulting in impaired cell-mediated immunity [5].

✉ Salim Ali Algaadi
s.algaadi@mu.edu.sa

[1] Department of Dermatology, College of Medicine, Majmaah University, Al-Majma'ah 11952, Saudi Arabia

HZ mainly appeared concurrently or after COVID-19 onset. However, HZ may precede the onset of COVID-19, being the first manifestation of COVID-19 disease. Therefore, herpes zoster may act as an indicator of latent COVID-19 infection [6, 7]. This should raise the suspicion of COVID-19 diagnosis in patients with asymptomatic HZ during this pandemic, which is of paramount importance in the management of COVID-19 and limiting the viral spread.

We present a literature review of HZ in patients with COVID-19, emphasizing their demographic data, clinical features, and associated immunological changes.

Material and methods

A literature search in Pubmed database and Scopus was conducted till 20th May 2021 using the following terms: 'Herpes zoster' or 'Varicella-zoster virus' and "COVID-19" or "coronavirus disease" or "SARS-CoV-2".

The search revealed 87 publications. We reviewed the titles and abstracts, as well as case descriptions.

The exclusion criteria included articles in a non-English language, no HZ reported, and HZ reported but unrelated

to COVID-19. Extensive manual searches were performed for papers from the references cited in the relevant papers.

We summarized the demographic and clinical data of patients, comorbidities, the treatment used, lymphocyte count, and distribution and timeline of HZ rash.

Results

After review, 14 articles met the inclusion criteria. A total of 29 patients had HZ associated with COVID-19. Patient age ranged from 7 to 82 years. Thirteen patients (45%) were men, and 16 (55%) women (Table 1). A rash involving trigeminal nerve distribution was observed in 12 patients (41.3%), of whom 7 were reported to have HZ ophthalmicus [8–12]. None of the cases had generalized HZ; however, one patient was reported to have multi-metameric involvement of the left scapular and right inguinal area [13]. Immunosuppression was reported in two patients: a 70-year-old man with cardiac transplant and a 70-year-old woman with myasthenia gravis and diabetes mellitus (on prednisolone and tacrolimus) [9, 14]. One patient was pregnant (32 weeks) [11]. The onset of HZ rash related to COVID-19-associated typical symptoms was variable, ranging from 2 days before COVID-19 symptoms to 70 days after the symptoms, averaging 17 days after COVID-19. Three patients (10%) had HZ rash presented preceding or concurrently with the classic COVID-19 symptoms [6, 15]. The most commonly reported comorbidities were hypertension and diabetes mellitus in 8 patients (27.5%) and 3 patients (10%), respectively [6, 12, 14–17].

Systemic antiviral medications were used to treat all patients, except two who were treated with analgesics only [6, 8–15, 18–20]. Intravenous acyclovir was used to treat 3 patients [8, 14, 18]. Famciclovir was used for one patient only [15]. Lymphocyte counts were reported in 15 patients, 13 (86.6%) of whom had lymphopenia.

Discussion

Several cutaneous manifestations of COVID-19 have been reported in the literature, making them important aids in the diagnosis of HZ [3, 5]. Moreover, HZ zoster cases were found to have increased during the COVID-19 pandemic [5].

Varicella-zoster virus (VZV) causes two known diseases, chickenpox and HZ; after primary VZV infection (chickenpox), VZV remains latent in human neurons for years; sufficient VZV-specific cell-mediated immunity (CMI) is necessary to maintain its latency [4].

The incidence of herpes zoster increases with age, with around 3 and 10 cases per 1000 in individuals aged 50 and 80, respectively [4], while other risk factors for HZ are CMI dysfunction (immunosuppressed individuals), diabetes, sex (female), genetic susceptibility, mechanical trauma, recent psychological stress, and Caucasian race [4]. The most commonly involved sensory nerves in VZV reactivation are trigeminal (cranial nerve), cervical and thoracic sensory nerves [4].

An increased incidence of HZ during the COVID-19 pandemic has been reported in a study from Brazil, with an overall Brazilian average increasing by + 35.4% during the pandemic (March to August 2020) when compared to the same interval in pre-pandemic period in the years of 2017 to 2019 [5]. HZ in the setting of COVID-19 pandemic has been reported in all age groups, including immunocompetent young children, 7 and 9 years old with HZ ophthalmicus [10].

We saw a high proportion of trigeminal nerve involvement (41.3%), with more than half of the patients suffering from HZ ophthalmicus. This makes timely diagnosis and prompt treatment essential to prevent ophthalmological complications.

The onset of HZ in relation to COVID-19 infection varied from 2 days before COVID-19 symptoms to 70 days after the onset of infection, averaging 17 days after COVID-19 infection. However, three patients (10%) had HZ rash that presented preceding or concurrently with the classic COVID-19 symptoms [6, 15]. Therefore, dermatologists and other clinicians should consider the diagnosis of asymptomatic COVID-19 in immunocompetent patients with HZ during the pandemic.

The treatments used were mainly oral acyclovir and valacyclovir [6, 8–15, 18–20]. However, intravenous acyclovir has been used for treating more severe disease [8, 14, 18]. Famciclovir was used for only one patient with a mild localized T4 dermatomal involvement HZ [15]. The response to treatment was good.

Three components of immune responses to VZV infection have been documented: innate immunity, humoral immunity, and cell-mediated immunity (CMI). All these components of immunity work against VZV infection, but the CMI is the most important part as it is needed to eliminate intracellular pathogen [4], which is evident in patients with defects in CMI where varicella and HZ are severe. Moreover, HZ is more frequent with increased age and more severe in T-cell-immunocompromised patients [21].

Lymphopenia is characteristically associated with COVID-19 infection, where T cells were found significantly reduced in numbers, and the surviving T cells were functionally exhausted [22]. Wang et al. analyzed the levels of lymphocyte subsets by flow cytometry in whole blood. They found that patients with COVID-19 had significantly lower total lymphocytes, $CD4^+$ T cells, $CD8^+$ T cells, B cells, and NK cells [23]. Moreover, a study investigating lymphocyte counts in HZ patients and healthy controls reported that

Table 1 Articles reported herpes zoster associated with COVID-19

Authors	Patients' age (years) and sex	Distribution	Onset in relation to COVID-19 infection	Comorbidities	Treatment	Lymphocyte Count
Ferreira, et al. 2020 [8]	39 M	Trigeminal	NR	Nil	Acylovir oral and intravenous	Lymphopenia
Tartari, et al. 2020 [9]	68 F 74 F 71 F 70 M	Trigeminal Trigeminal Trigeminal The dorsum of hand	NR	NR	Acylovir	Lymphopenia
Elsaie, Youssef, and Nada 2020b [6]	68 M 60 F	right loin Left side of chest and nape of the neck	2 days before Simultaneous	HTN and Dyslipidemia HTN	Valacyclovir Acyclovir	NR
Xu, et al. 2020 [18]	73 M	right lateral arm, shoulder and neck	36 days after	NR	intravenous acyclovir	NR
Nofal, et al. 2020 [10]	42 M 7 F 28 M 9 M	Herpes zoster ophthalmicus	4 days after 5 days after 5 days after 4 days after	NR	Oral acyclovir	Lymphopenia
Elsaie, Youssef, and Nada 2020a [11]	36 F	Lt forehead and upper eyelid	7 days after	Nil	Valacyclovir Acetaminophen	
Cao, et al. 2020 [14]	70 F	Right side of the waist	46 days after	Type 2 diabetes and myasthenia gravis	Aciclovir 0·5 g intravenous	Lymphopenia
Brambilla, et al. 2020 [13]	68 F 44 F 64 F	Multi-metameric((left scapular and right inguinal) Intercostal Thoraco-abdominal	8 weeks 8 weeks 10 weeks	NR	Valacyclovir Valacyclovir Only paracetamol	Lymphopenia
Saati, et al. 2020 [15]	57 M	Thoraco-dorsal with residual neuralgia	simultaneous	HTN	Famciclovir	NR
Fernandez-Nieto, et al. 2020 [12]	56 F[1212121212121212] 52 M 63 F 56 M 82 M 73 F 78 M	Localized (not specified) Localized (not specified) Ophthalmic Ophthalmic Localized (not specified) Localized (not specified) Localized (not specified)	22 days after 14 days after 26 days after 26 days after 7 days after 12 days after 6 days after	Nil Nil HTN Dyslipidaemia HTN, DM Dyslipidaemia HTN	Valacyclovir Valacyclovir Valacyclovir Valacyclovir Acyclovir Acyclovir Acyclovir	NR
Shors 2020 [19]	49 F	Trigeminal	1 week after	Nil	Valacyclovir	NR
Elsaie and Nada 2020 [20]	44 M	Left upper chest and back	1 week after	NR	Valacyclovir	NR
Pona, et al. 2020 [16]	70 F[1616161616161616]	Left hip	1 week after	HTN DM	Gabapentin No antiviral	Normal Lymphocyte Count
Desai, et al. 2021 [17]	62 F	Right lower abdomen in an iliac region	20 days after	HTN	Acyclovir	Normal Lymphocyte Count

DM diabetes mellitus, *F* female, *HTN* hypertension, *M* male, *F* female, *NR* not reported

$CD3^+$ T cells, $CD4^+$ T cells and $CD8^+$ T cells were significantly lower in the HZ group [24].

This, in turn, is known to favor the reactivation of VZV, resulting in HZ [4]. It is thought that the occurrence of HZ infection correlates with a drop in the threshold of VZV-specific CMI below an unknown level, while the severity of HZ correlates with the remaining level of this VZV-specific CMI at the time of reactivation [4]. So, this hypothetically can cause the increased occurrence of HZ and more severe disease in patients with COVID-19 infection.

Lymphopenia was present in 13 (86.6%) of patients where lymphocyte counts were reported [8–10, 13, 14, 16, 17]. This could make them vulnerable to VZV reactivation and HZ. Physicians should be aware of such an association between HZ and COVID-19 infection, which is possible in a few weeks following COVID-19 infection and diagnose and treat HZ early to prevent complications, especially when a considerably large proportion of HZ involves the trigeminal nerve and HZ ophthalmicus [8–12].

In 2006, herpes zoster vaccine was licensed and in 2008 it was advised to be used for people aged 60 years or more to prevent HZ and its complications including [25]. With increased age, not only the risk of HZ increases but also the risk of its complications including post-herpetic neuralgia, hospitalizations and impaired daily activities [25]. Efficacy of HZ vaccine for prevention of HZ and PHN were studied on a large scale of population [26]. In a randomized controlled trial which followed 38,546 subjects for up to 4.9 years after vaccination found a vaccine efficacy of 51.3% for prevention of herpes zoster and 66.5% for prevention of PHN [26].

Given its favorable safety profile and high efficacy, HZ vaccine should be recommended for all elderly and during the pandemic with the overload of health services, the risk of catching COVID-19 infection while in hospital and the possible increased incidence of HZ during the pandemic makes HZ vaccine essential for given its favorable safety profile and significant efficacy.

Moreover, we believe that zoster vaccination should be considered during this pandemic, especially for the elderly and fragile patients, to prevent HZ and its considerable morbidity in this subset of patients.

A limitation of our study is that the number of reports and the available data was not sufficient to draw strong, generalizable conclusions. However, based on the available data, reports of an increased number of HZ cases during the COVID-19 pandemic, and the lymphopenia associated with COVID-19 infection, which favours VZV reactivation, we think that there is a causal relationship between COVID-19 infection and HZ. Nevertheless, such a causal relationship needs further epidemiological studies for confirmation. We hope our study paves the way for further studies on this topic. We also emphasize the importance of the available, safe and very effective HZ vaccine for elderly, fragile and immunocompromised people during the COVID-19 pandemic which can prevent the debilitating HZ and its complications and save them from the need for the currently overwhelmed health services.

Funding None.

Declarations

Conflict of interest The author declares that they have no conflict of interest.

References

1. Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. JAMA. 2020;323:709–10.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2001017
3. Rahimi H, Tehranchinia Z. A comprehensive review of cutaneous manifestations associated with COVID-19. BioMed Res Int. 2020;2020:1–8.
4. Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol. 2010;48:S2–7.
5. Maia CMF, Marques NP, de Lucena EHG, de Rezende LF, Martelli DRB, Martelli-Júnior H. Increased number of Herpes Zoster cases in Brazil related to the COVID-19 pandemic. Int J Infect Dis. 2021;104:732–3.
6. Elsaie ML, Youssef EA, Nada HA. Herpes zoster might be an indicator for latent COVID 19 infection. Dermatol Therapy. 2020;33:e13666.
7. Adam I. Is herpes zoster being an indicator for COVID 19 infection? Dermatol Therapy. 2020. https://doi.org/10.1111/dth.13846
8. Ferreira AdF, Romão TT, Macedo YS, Pupe C, Nascimento OJ, Neurology FotAAo. COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy. Eur J Neurol. 2020;27:1748–50.
9. Tartari F, Spadotto A, Zengarini C, et al. Herpes zoster in COVID-19-positive patients. Int J Dermatol. 2020;59:1028–9.
10. Nofal A, Fawzy MM, Deen SMSE, El-Hawary EE. Herpes zoster ophthalmicus in COVID-19 patients. Int J Dermatol. 2020;59:1545.
11. Elsaie ML, Youssef EA, Nada HA. Herpes zoster may be a marker for COVID-19 infection during pregnancy. Cutis. 2020;106:318–20.
12. Fernandez-Nieto D, Ortega-Quijano D, Suarez-Valle A, Burgos-Blasco P, Jimenez-Cauhe J, Fernandez-Guarino M. Comment on: "To consider varicella-like exanthem associated with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out. Characterization of herpetic lesions in hospitalized COVID-19 patients." J Am Acad Dermatol. 2020;83:e257–9.
13. Brambilla L, Maronese CA, Tourlaki A, Veraldi S. Herpes zoster following COVID-19: a report of three cases. Eur J Dermatol. 2020;30:754.
14. Cao X, Zhang X, Meng W, Zheng H. Herpes zoster and postherpetic neuralgia in an elderly patient with critical COVID-19: a case report. J Pain Res. 2020;13:2361.

15. Saati A, Al-Husayni F, Malibari AA, Bogari AA, Alharbi M. Herpes zoster co-infection in an immunocompetent patient with COVID-19. Cureus. 2020. https://doi.org/10.7759/cureus.8998.
16. Pona A, Jiwani RA, Afriyie F, Labbe J, Cook PP, Mao Y. Herpes zoster as a potential complication of coronavirus disease 2019. Dermatol Therapy. 2020. https://doi.org/10.1111/dth.13930.
17. Desai HD, Sharma K, Patoliya JV, Ahadov E, Patel NN. A rare case of varicella-zoster virus reactivation following recovery from COVID-19. Cureus. 2021. https://doi.org/10.7759/cureus.12423.
18. Xu R, Zhou Y, Cai L, et al. Co-reactivation of the human herpesvirus alpha subfamily (herpes simplex virus-1 and varicella zoster virus) in a critically ill patient with COVID-19. Br J Dermatol. 2020;183:1145–7.
19. Shors AR. Herpes zoster and severe acute herpetic neuralgia as a complication of COVID-19 infection. JAAD Case Rep. 2020;6:656–7.
20. Elsaie ML, Nada HA. Herpes zoster (shingles) complicating the course of COVID19 infection. J Dermatol Treat. 2020. https://doi.org/10.1080/09546634.2020.1782823.
21. Sartori AMC. A review of the varicella vaccine in immunocompromised individuals. Int J Infect Dis. 2004;8:259–70.
22. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827.
23. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. 2020;221:1762–9.
24. Wei L, Zhao J, Wu W, et al. Decreased absolute numbers of CD3+ T cells and CD8+ T cells during aging in herpes zoster patients. Sci Rep. 2017;7:1–8.
25. Hales CM, Harpaz R, Ortega-Sanchez I, Bialek SR. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly Rep. 2014;63:729.
26. Oxman MN, Levin MJ, Johnson G, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271–84.