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Herpes zoster in the era of COVID 19: A prospective observational study to probe the association of herpes zoster with COVID 19 infection and vaccination

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Abstract

Herpes zoster (HZ) is caused by reactivation of the latent varicella zoster virus (VZV) following decline in cell-mediated immunity. All over the world, in the past couple of years, the Corona Virus 2019 (COVID-19) has emerged as a viral cause of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection. Based on the current limited evidence, co-infection of COVID-19 with VZV or reactivation of VZV after COVID-19 vaccination has been sporadically reported. All patients diagnosed with HZ, in Farwaniya Hospital in Kuwait, from March 2020 to July 2021, having either (A) a positive COVID-19 polymerase chain reaction (PCR) test, or (B) been vaccinated against SARS-CoV-2 were enrolled in the study. All patients' demographic information, medical history, laboratory findings, and vaccination status was documented. All statistical analyses were performed using SPSS Statistics version 21.0 software. Twelve cases infected with COVID-19 with a positive PCR (group 1) and five cases vaccinated against SARS-CoV-2 (group 2) were documented. Out of the 12 COVID-19 infected patients (group 1), only two patients (16.67%) required hospitalization, while the remaining 10 patients had mild/moderate lymphopenia. Furthermore, amongst the 12 positive COVID-19 cases, four patients with HZ were diagnosed within the first week of COVID-19, while the remaining eight cases were diagnosed within 8 weeks of COVID-19. Thoracic segments were affected in five cases (41.67%), cervical in one case (8.33%), cranial in two cases (16.67%), lumbar in three cases (25%) and sacral in one case (8.33%). In group 2, three patients presented with HZ within 4 weeks of having received the first dose of the vaccine and two patients after the second dose. Blood investigations for all five vaccinated patients did not show any abnormalities. Cervical segments were affected in two patients (40%), and cranial, thoracic, and lumbar segment in the remaining patients respectively (20%). Experts must be aware of the probable increased risk of HZ during the COVID 19 pandemic. We propose appropriate curative and preventive measures against HZ infection, including a systematic follow-up of these patients to ensure that they stick to extreme safety measures till the diagnosis of COVID-19 is omitted.

KEYWORDS
COVID 19, herpes zoster, mRNA vaccine

1 | INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been recognized as a pandemic by the World Health Organization (WHO).[1] The disease was acknowledged as COVID-19 (Coronavirus Disease 2019), and has become a public health hazard in almost every country across the world.[1] The disease most commonly manifests within the fifth day of exposure to the virus, but the incubation period can be as long as 14 days in some cases. The clinical features seen in patients with COVID-19 can be highly variable, with few cases being completely asymptomatic. Majority of the symptomatic patients tend to develop milder symptoms, only 10%–15% develop severe symptoms requiring hospitalization, and approximately 10% of these severe cases may eventually succumb to the disease.[2] Thus, the clinical situation varies widely, with the majority of patients needing only supportive treatment, whereas others require admission to intensive care unit (ICU) for invasive mechanical ventilation or hemodynamic monitoring.[3] The diagnosis of COVID-19 disease is based on the clinical signs (fever, malaise, fatigue, dry cough, rhinorrhea, anosmia, dyspnea, anorexia, and diarrhea), vital signs (fever >38.0°C, pulse oximetry saturation <95%), and radiological findings (chest CT scan for the presence of ground glass opacity).[3] The diagnosis can be confirmed by detection of viral RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swabs or bronchoalveolar fluid.[4] Coronavirus disease 2019 (COVID-19) primarily presents with pulmonary symptoms, yet extrapulmonary symptoms involving cutaneous manifestations have been identified. Cutaneous manifestations in COVID-19 patients involve chilblain-like eruption (covid toe), petechiae and purpura, vesicles, urticaria, livedo reticularis, chicken-pox like lesions and erythematous maculopapular lesions and several other distinct patterns.[5,6] This might be due to direct immune damage by SARS-COV2, or indirectly as an indicator of systemic involvement.[7,8]

Varicella zoster virus (VZV) is a human neurotropic virus that causes varicella. Herpes zoster (HZ) is an acute, viral infection which ensues after the reactivation of the VZV. The virus usually remains dormant inside the sensory ganglia, notably, the dorsal root ganglia, trigeminal ganglia, and enteric ganglia after the virus's initial exposure in the form of chicken pox infection.[9] The latent phase usually lasts for several decades before reactivation occurs. HZ possibly appears when the immune system fails to contain the dormant VZV replication. Consequently, it often occurs in the elderly people, HIV-infected patients, and is more common in severely immunocompromised patients. Trauma, radiation, certain medications, and stress, can similarly trigger HZ but have not been determined with certitude.[10,11]

HZ is characterized by occurrence of multiple, painful, unilateral vesicles and ulceration, and typically limited to a single dermatome innervated by single dorsal root or cranial sensory ganglion.[12]

COVID-19 infection may represent a trigger for HZ reactivation. Among the COVID-19 pandemic, several published laboratory-confirmed COVID-19 reports with coexisting clinical manifestations of HZ virus have been reported, suggesting a probable co-existence of the two viruses, or an increased frequency of HZ in this population.[13–21]

COVID-19-associated lymphopenia, especially CD3 + CD8 +- lymphocyte and functional impairment of CD4 + T cells, can render COVID patient more prone to evolving HZ by reactivating VZV.[22] It is also stated that HZ might be an indication of undiagnosed COVID-19 infection in younger age groups.[13,18,23]

In a challenge to lessen the morbidity and mortality associated with COVID-19 and halt viral transmission, a variety of vaccines has been developed. Among these vaccines, messenger RNA (mRNA) vaccines that supposedly provide up to 95% protection from COVID-19 after a two-dose series have been prepared.[24] Common vaccine-related side effects including pain, redness, and/or swelling at the injection site, fatigue, headache, fever, and chills have been commonly reported.[24] HZ reactivation was reported following trivalent influenza, hepatitis A and rabies vaccines, suggesting vaccine-mediated immunomodulation.[25] Several reports have demonstrated cases of VZV reactivation developing after vaccination with the mRNA COVID-19 vaccine.[26,27]

The aim of the report is to investigate clinical presentations of HZ infection in the era of Covid infection and mRNA-COVID 19 vaccination.

2 | MATERIALS AND METHODS

All patients diagnosed with HZ in Dermatology Department outpatient Clinics, Farwaniya Hospital in Kuwait, from March 2020 to July 2021, having either (A) a positive COVID-19 PCR test or (B) have been vaccinated against SARS-CoV-2 were enrolled in the study. A total of 17 patients were enrolled, 12 were infected with COVID 19 (RTPCR positive), while the remaining were vaccinated against SARS-CoV-2. All patients' demographic information (patient age, sex), medical visit type (including COVID-19 inpatient, or outpatient status), medical history, symptoms, severity assessment, laboratory findings, chest computed tomography (CT) or radiograph findings, treatment regimens, and treatment efficacy for COVID-19 infected patients or vaccination status was documented.

Patients were divided into two groups; HZ patient with up to 8 weeks after COVID-19 infection (group 1) and HZ patients within 4 weeks after COVID vaccination either first dose or second dose of mRNA vaccination (group 2).

Categorical data were described as percentages and continuous data as median with interquartile range (IQR). Statistical analysis was completed using chi-squared tests to determine a significant relationship between those with HZ and COVID-19 infection or vaccination. All statistical analyses were performed using SPSS Statistics version 21.0 software.

3 | RESULTS

A total of 12 cases were documented in Covid infected group (group 1) and five cases in the vaccinated group (group 2). The mean age of patients was 53 years in group 1 and 37 years in group 2. The age ranged from 24 to 76 years for both groups. The male: female ratio

TABLE 1 Demographic characteristics of patients

Study population	Covid group no. (%)	Vaccinated group no. (%)
No. of patients	12	5
Male:female ratio	1.4:1	0.67: 1
Male	7 (58.33%)	2 (40%)
Female	5 (41.67%)	3 (60%)
Age, median (IQR), y	53 (37–75)	39 (24–67)
Highest patient temperature, median (IQR), °C	38.9 (38.5–41.0)	37.6 (37–38.5)
Initial common symptoms		
Fever	11 (91.67%)	0
Cough, dry	5 (41.67%)	0
Cough, productive with sputum	2 (16.67%)	0
Dyspnea	3 (25%)	0
Myalgia or fatigue	7 (58.33%)	3 (60%)
Headache	4 (33.33%)	4 (60%)
Nasal symptoms	1 (8.67%)	0
Diarrhea	1 (8.67%)	0
Chest imaging		
5 (41.67)	5 (41.67%)	NA
Unilateral infiltrate	2 (16.67%)	NA
Prior comorbidities		
Hypertension	1 (8.67%)	0
Diabetes	1 (8.67%)	1 (20%)
Chronic obstructive pulmonary disease	2 (16.67%)	0
Therapy		
Oxygen therapy	1 (8.67%)	0
Methylprednisolone	2 (16.67%)	0
Antibiotic	9 (75%)	0
Antiviral	12 (100%)	5 (100%)
Other supportive treatments	9 (75%)	2 (40%)

Abbreviation: IQR, interquartile range.

TABLE 2 Laboratory results of patients with COVID-19 infection

Characteristic	Range in patients	Normal range
Blood count, $\times 10^9$/L, median (IQR)		
Lymphocyte	0.917 (0.67–1.3)	1.1–3.2
Leukocyte	4.6 (3.5–6.4)	3.5–9.5
Neutrophil	2.3 (1.9–4.7)	1.8–6.3
Platelet	196 (121–237)	125–350
Hemoglobin (g/L)	127.5 (103–145)	130–170
Inflammatory indicators, median (IQR)		
ESR, (mm/h)	27 (13–45)	0–15
Interleukin-6, (pg/ml)	15 (6–31)	0–7
C-reactive protein, (mg/L)	35 (8–59)	0–10
Blood biochemistry		
Glucose, mM	5.9 (4.9–7.6)	3.9–6.1
Alanine aminotransferase (U/L)	38·0 (21–67)	9–50
Aspartate aminotransferase (U/L)	31 (18–59)	15–40
Blood urea nitrogen (mmol/L)	5·3 (3.6–8.1)	3.6–9.5
Serum creatinine (μmol/L)	74·8 (62–98)	57–111

Abbreviations: ESR, erythrocyte sedimentation rate; IQR, interquartile range.

was 1.4:1 (7 male:5 female) in group 1 and 0.67: 1 in group 2 (2 male:3 female). In group 1, the highest number of cases (5 cases = 41.67%) were seen in the age group between 41 and 50 years, while in group 2, 60% (3 cases) were seen in the age between 31 and 40 years. The age and sex distribution are given in Table 1.

3.1 | Symptoms and signs of COVID 19 disease (Group 1)

The diagnosis of coronavirus disease was confirmed in all cases by doing a RT-PCR test for COVID-19 on nasopharyngeal swabs. The most commonly reported symptoms at onset of illness were fever 11(91.67%) patients, cough, either dry 5(41.67%) patients, or productive in 2(16.67%), dyspnea in 3(25%), fatigue or myalgia in 7 (58.33%), headache in 4(33.33%) patients, and anosmia, gastric upset, and diarrhea in 1(8.67%) patient each.

A total of 5(41.67%) patients had findings of bilateral infiltrates on radiographic imaging, while 2(16.67%) patients had unilateral infiltrates. Four (33.33%) patients had co-morbidities, including hypertension in one (8.67%) patient, diabetes in one (8.67%) patient, and chronic lung disease in two (16.67%) patients. Of the 12 patients, only two patients (16.67%) required hospitalization due to complications of bilateral interstitial pneumonia, and one (8.67%) patient required oxygen support in the hospital for short time. Methylprednisolone was given to only 2 patients (16.67%). (Table 1). Most patients (9 [75%]) received empirical antibiotic treatment and supportive therapy.

Laboratory findings for covid patients are summarized in Table 2. Complete blood count revealed that most of the patients, 10 (79.24%) had mild/moderate lymphopenia with a mean lymphocyte count of 0.917×10^9/L (normal value: $1.1–3.2 \times 10^9$/L for adults), and anemia in seven (58.33%) patients. Furthermore, four (33.33%) patients had leukopenia. Platelets count was found to be reduced in two (16.67%) patients, while no change was noticed in neutrophil values.

Regarding inflammatory indicators, both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was raised in nine (75%) patients, and interleukin-6 (IL-6) was high in eight (66.67%) patients. Some patients demonstrated liver injury with elevated aspartate amino transferase (AST; 2[16.67%]) and alanine amino transferase

(ALT; 3 [25%]). Kidney profile (blood urea and creatinine) was normal in all the patients.

Evaluating the levels of lymphocyte subsets by flow cytometry, in whole blood of COVID-19 patients indicated that there was reduction in range of various lymphocyte subclasses ($CD3^+$ T cells, $CD4^+$ T cells and $CD8^+$ T cells). However, the CD4+/CD8+ ratio did not change significantly over the course of the illness. (Table 3).

3.2 | Symptoms and signs of VZ infection

3.2.1 | In covid infected group ($n = 12$ patients)

Four HZ patients were diagnosed concurrently or within the first week of COVID-19 diagnosis, while the remaining eight cases occurring within 8 weeks of COVID-19 infection (Chart 1). The details of the segmental (dermatomal) distribution of HZ seen in this group is displayed in Chart 2. Thoracic segments were the most commonly involved, seen in 5 (41.67%) cases, cervical in 1 (8.33%), cranial in 2 (16.67) cases, lumbar in 3 (25%) cases and sacral in 1 (8.33%) case. Zoster related pain was perceived in eight (66.67%) cases, with the highest prevalence of pain seen in the 51–60 years age group in nine out of the 12 (75%) patients in group 1. Out of the 12 patients in covid infected group, three (25%) patients developed complications. The complications observed were secondary bacterial infection (two patients, 16.67%), severe ulceration (one patient, 8.33%). No scarring, PHN or motor weakness was noticed on follow-up. (Table 2). In terms of treatment, nine patients received valacyclovir 1gm three times daily and three patients received Acyclovir 800 mg five times daily, both for 7 days, along with scheduled COVID-19 treatment.

TABLE 3 Lymphocyte subpopulation counts of Covid-19 patients

Lymphocytes × 10^6/L	Value
CD3+	691 ± 526
CD4+	389 ± 364
CD8+	328 ± 197
CD4+/CD8+	1.41 ± 0.59

3.2.2 | In the vaccinated group ($n = 5$ patients)

Three patients developed HZ after the first dose of the vaccine and two patients after the second dose (Chart 1). Four patients were healthy adults less than 45 years, while the fifth patient was 67 years old. Blood investigations for all five patients did not show any abnormalities. Two patients had significant constitutional symptoms such as fever, headache, and arthralgia, 2–3 days prior to or concurrently with the appearance of HZ vesicles. Pain preceded the vesicles in 4 (80%) cases. The highest prevalence of pain (80%) in group 2 was seen in the 31–40 years age group.

All patients experienced segmental neuralgia at some point in time during the course of the disease, varying in intensity from mild to very severe. One patient had preherpetic itching started 2–3 days preceding the lesions. No complications developed in any of the five recruited patients in group 2.

The dermatomal distribution of the skin lesions is shown in Chart 2, and it revealed that the cervical segments were affected in two patients (40%), cranial segment in one patient (20%), thoracic segment in one patient (20%) and lumbar segment in one patient (20%). In terms of treatment, all five patients received Acyclovir 800 mg five times a day for 7 days. In conclusion, all 17 cases in both groups had

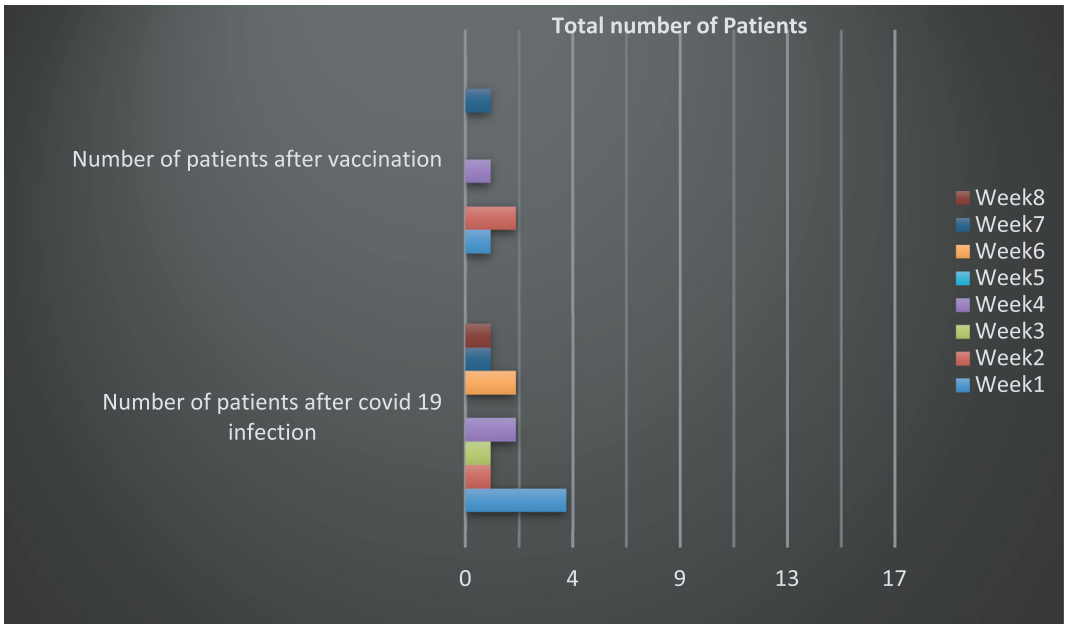
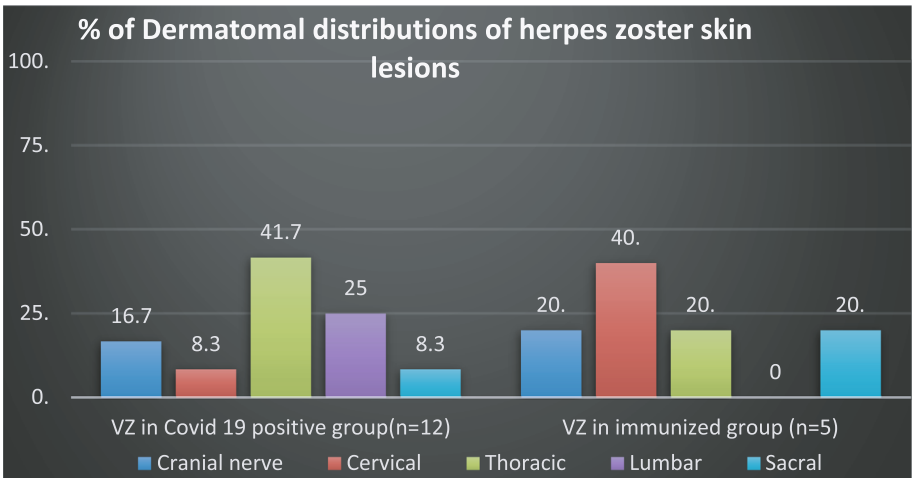


CHART 1 Period until HZ diagnosis. HZ, herpes zoster

CHART 2 Percentage of dermatomal distributions of herpes zoster skin lesions



only one or two dermatomal involvements. None of the patient complained of postherpetic neuralgia.

4 | DISCUSSION

Few studies done on COVID 19 have addressed mixed viral infections in systematic fashion. The data related to multiple infections were usually derived incidentally for the purpose of the investigations.[28] The occurrence of multiple virus infections in a patient is not an unusual finding. There was no indication that mixed infections were associated with increased disease risk in immunocompetent patients or in certain immunocompromised patients.[28]

COVID-19, caused by the pathogen SARS-CoV-2, was declared a pandemic by World Health Organization in March 2020. The diagnosis can be confirmed by detection of viral RNA by RT-PCR in the samples obtained from nasopharyngeal swabs or bronchoalveolar fluid. Arising signs advocate that COVID-19 not only involves the respiratory system but can affect several organ systems including the skin. COVID-19-associated cutaneous manifestations have been increasingly reported in recently published studies.[29] COVID-19's cutaneous symptoms appear in patients of all ages with differing levels of severity. An increase in awareness and identification of these cutaneous manifestations by physicians may be vital to ensure an earlier and more accurate diagnosis, possibly resulting in better prognosis in COVID-19 patients.[30]

A report from Italy[31] disclosed a high percentage of skin manifestations (20.4%) present in COVID-19 positive patients after excluding those that had used any new medication in the preceding 2 weeks.[31] On the contrary, a study from China contrasted this high result, disclosing cutaneous manifestations in only 0.2% of its COVID 19 patients.[32] To date, it is not possible to establish the exact incidence of skin lesions in COVID-19.[33] Despite an increase in significance, much remains unknown regarding the characterization, incidence, and pathogenesis of these dermatological symptoms.[30] The role of skin manifestations, where present, in the clinical history of COVID-19 is still unclear. In 75% of patients with cutaneous manifestations, the skin lesions appeared before the other typical clinical manifestations of COVID-19.[33]

Currently, the association between HZ and COVID-19 is unknown. Since the emergence of the COVID-19 pandemic, numerous issued scientific papers observed and globally reported increased number of cases of HZ infections during the COVID-19 outbreak, proposing a probable co-existence of the two viruses, or an increased prevalence of HZ in the context of COVID-19 infection and vaccination.

A Brazilian study[34] compared the data from the public database (DATASUS) of Brazil's Ministry of Health on the number of diagnoses of HZ from March to August from 2017 to 2019, with the same period in 2020. The authors observed an increase in the number of HZ over the years and the negative impact from the COVID-19 disease, revealing an average increase corresponding to an extra 10.7 cases per million inhabitants during the current pandemic, which suggests a correlation between these diseases.[34]

The incubation time of COVID-19 can be up to 14 days and the majority of cases only exhibit mild to moderate symptoms.[35] Elsaie et al.[15] described two cases of HZ reactivation preceding the appearance of COVID-19 respiratory symptoms. Patients were treated with valacyclovir or acyclovir and had good prognosis. They suggested that the clinical presentation of HZ at the time of the current pandemic even in patients giving mild or no suggestive history of upper respiratory symptoms should be considered as an alarming sign for a recent subclinical SARS CoV2 infection. HZ infection may be an alarming sign of a subclinical COVID-19, even in patients with mild or no respiratory symptoms during the pandemic period.[15]

The first series on this varicella-like exanthem as a specific COVID-19–associated cutaneous feature was perceived by Marzano et al.[36] during the Italian outbreak in 2020. They spotted a varicella-like papulovesicular exanthem as a rare but specific COVID-19–associated skin manifestation in 22 patients including one child. Eight Italian dermatology units collected clinical data from patients with COVID-19 (microbiologically proven by nasopharyngeal swab) and no history of new medications in the previous 15 days who developed varicella-like lesions. Its typical features were frequent trunk

involvement, usually scattered distribution, and mild/absent pruritus.[36] Compared to the Italian study, the lesions of our COVID-19 patients were associated with less itching, and were mostly found on trunk and limbs and rarely on the face.

Another Spanish study series,[37] described 15 patients with laboratory-confirmed COVID-19 concomitant with reactivated HSV or HZ. Seven had localized HZ; two of whom presented with HZ ophthalmicus. The latency time between the onset of COVID-19 symptoms and herpes skin lesions was 6–32 days. SARS-CoV-2 was not detected in the vesicle fluid of three patients who underwent RT-PCR testing.[37]

Tartari et al.[13] reported four HZ infections in COVID-19-positive patients, three female, one male, with median age of 70.5 years. The four patients showed leukopenia at the time of diagnosis. Three patients were admitted to the ICU and developed a necrotic HZ on the second branch of the trigeminal nerve, while the fourth case showed the classic HZ characteristics. Patients were prescribed the standard acyclovir dosage with routine COVID-19 treatment. All cases were managed without postherpetic neuritis.[13]

Nofal et al.[14] presented four patients, two children and two young adults, aged 7–42 years with laboratory-confirmed COVID-19 who developed HZ ophthalmicus (HZO) few days after COVID-19 diagnosis. The patients were immunocompetent and had mild to moderate COVID-19 disease manifestations. HZO is rarely reported in childhood, particularly in immunocompetent children. They were effectively managed as outpatient cases with supportive and symptomatic treatment for COVID-19, in addition to acyclovir. They proposed that HZO might be an indicator of COVID-19 infection, particularly in young, immunocompetent patients.[14]

Several isolated case reports have been published from different countries spread across the world, about the reactivation of HZ in COVID-19 patients, causing the raised concerns of the possible association.

Shors et al.[16] reported a 49-year-old female with concurrent COVID-19 and HZ, which emerged on the seventh day since the onset of COVID-19 symptoms. The patient was treated with valacyclovir 1 g three times daily. The skin lesions had a slow response to therapy, and she developed severe neuralgia, fairly controlled with oral gabapentin and topical lidocaine.[16]

Similarly, a 39-year-old man with laboratory-confirmed COVID-19, and with no past medical history developed cutaneous HZ lesions in the left trigeminal nerve distribution and responded well to the treatment, 5 days after IV administration of acyclovir 10 mg/kg.[18]

Another case of 70-year-old woman with laboratory-confirmed COVID-19, a history of type 2 diabetes, and myasthenia gravis, presented HZ skin lesions. The patient was discharged after treatment with intravenous acyclovir 250 mg three times a day for 16 days, followed by oral acyclovir 400 mg five times daily for 7 days. Nevertheless, she acquired postherpetic neuralgia and responded poorly to treatment.[19]

Desai et al.[21] reported reactivation of HZ in a woman that had recently recovered from COVID-19, as evident from her negative RT-PCR for COVID-19 with negative immunoglobulin M (IgM) antibody and positive immunoglobulin G (IgG) antibody for COVID-19 at the time of presentation with HZ. Her white blood cell (WBC) counts were within normal range and there were no signs of immunosuppression.[21]

Saati et al.,[22] described a case of HZ, 2 days after developing respiratory symptoms in a 57-year-old immunocompetent man. All his vital signs and physical examination were normal except for vesicles with surrounding erythema, localized to an area consistent with T4 dermatome. The authors acknowledged that throughout the period of the COVID-19 pandemic, patients presenting with HZ, may warrant healthcare workers to rule out COVID-19 and apply maximum personal protective equipment when treating such patients.[22]

Elsaie et al.[23] reported a 27 weeks pregnant woman with painful, itchy, papules and vesicles on the left side of her forehead. The clinical diagnosis of HZ was made. A positive nasopharyngeal smear RT-PCR report was consistent with COVID-19 infection. They suggested that the clinical presentation of HZ at the time of the current pandemic, especially if associated with other signs of COVID-19 infection, should be carefully monitored and reported for further assessment.[23]

Packwood et al.[38] described a 58-year-old patient with a diagnosis of meningitis and cutaneous manifestations of HZ, who had laboratory-confirmed COVID-19. At the time of admission, the patient received famciclovir for 6 days, and then intravenous acyclovir besides to meningitis treatment. She was discharged after a month, in stable condition.[38]

Ayaz et al.[39] reported a disseminated HZ infected patient, with laboratory-confirmed COVID-19. The patient was discharged in good general condition after effective treatment. However, the authors did not mention the details of the treatment regimen.[39]

Additionally, Pona et al.[40] reported a 70-year-old woman with laboratory-confirmed COVID-19 and HZ, who had presented with numerous vesicles and hemorrhagic crusted lesions on the left hip and superior buttock. She had no lymphopenia. This patient, despite having hypertension and complicated type 2 diabetes mellitus, was treated effectively with only gabapentin for her pain relief, and without any kind of antiviral therapy.[40]

Lymphocytes and their subsets perform a significant role in the maintenance of immune system function. Alongside immune diseases and other infectious disease, virus infection can also lead to dysregulation in the levels of lymphocyte subsets.[41,42]

Virus particles spread across the respiratory mucosa and infect additional cells, produce a series of immune responses, and cause variations in peripheral WBCs and immune cells such as lymphocytes.[43]

The basis for the increased vulnerability to HZ reactivation in COVID-19 patients most likely points toward the tendency of COVID-19 virus to produce an immunosuppressive state secondary to the functional impairment, and the relative quantitative decrease in T lymphocytes, particularly CD4+ T cells, CD8+ T cells, and natural killer cells.[44]

It was confirmed that COVID-19 infection is associated with a decrease in lymphocytes, monocytes, and eosinophils, along with a significant reduction of CD4/CD8 T cells, B cells, and natural killer cells. It was further disclosed that non-survivor COVID-19 patients

continued to show a reduction in lymphocyte counts along the course of their disease until death.[45–47]

According to our patient's laboratory tests, the total value of lymphocytes in 10 patients in COVID-19 infected group was reduced, indicating an impairment of the immune system during the course of COVID-19 infection, which might have effect to the termination of varicella dormancy. In our patients, these findings persisted for several weeks after COVID-19, which may have led to VZV reactivation.

In some reported cases, as well as in our patients, both lymphopenia and decrease in absolute lymphocyte number, especially CD3+, CD4+, and CD8+ T cells due to SARS-CoV-2 infection were observed.[13,15] Thus, lymphopenia and decreased CD4 + T cells, might possibly lead to impaired antiviral response.[15] Hence, other viral infections may occur with COVID-19. Some studies propose that COVID-19 infection causes a significant decrease in the total number of lymphocytes, indicating that coronavirus consumes many immune cells and impedes the body's cellular immune function.[48]

Certainly, COVID-19 infection has been shown to be able to reactivate numerous viruses, including human herpesvirus-6, 7, and Epstein–Barr virus as revealed in a recent case of pityriasis rosea during COVID-19.[49]

Different mechanisms for lymphocyte exhaustion and deficiency were speculated among COVID-19 patients and include direct lymphocyte death via coronavirus angiotensin-converting enzyme 2 lymphocyte expressed receptors. Another hypothesized mechanism that still requires to be further explored was direct damage to lymphatic organs, such as the thymus and spleen. Also, direct lymphocyte apoptosis mediated by tumor necrosis factor-α, IL-6, and other pro-inflammatory cytokines; and direct inhibition of lymphocytes by metabolic disruption, such as acidosis have also been considered.[8,50]

Reactivation of VZV is a failure of the T cell component of the immune system to sustain control of the infection. It also has been hypothesized that the functional damage of CD4+ T cells may predispose patients with COVID-19 to severe disease.[44] Such immune variations can render a patient more vulnerable to developing shingles by reactivating VZV, which might be a mark of undiagnosed COVID-19 infection in younger age groups.

Intensified psychological stress can precipitate the occurrence of HZ. As COVID-19 survivors can suffer from remarkable psychological stress, they may be at risk of HZ.[51] Pona et al.[40] reported a HZ case who had a normal absolute lymphocyte count. They postulated that the increased psychological stress from COVID-19 may explain her reactivated zoster, despite the presence of normal lymphocyte count which argues against decreased cell-mediated immunity as the cause of HZ. Consequently, COVID-19 patients with a normal lymphocyte count may still be at risk of HZ reactivation.[40]

HZ is a cause of considerable morbidity, especially in elderly or critically ill patients. Most of our patients were immunocompetent with no co-morbidities. Assumed the absenteeism of any of the well described predisposing factors in our patients which may have lead to reactivation of HZ, it appears that COVID-19 infection, as a critical illness with its related physical and emotional stress, could represent the triggering factor for the development of HZ.

In COVID-19, the minority of cases present with severe symptoms and a hyper-inflammatory state.[52] Once a body is exposed to a foreign microbe, activation of the pattern recognition receptors presented on the surface of the immune cells directs the host to initiate a sepsis-like response.[53]

Annotations on patients with mild disease have demonstrated a meaningfully decreased T cell and CD8 levels, indicating a possibility of SARS-CoV-2 directly infecting lymphocytes, which is ultimately represented in dysfunctional antiviral effects.[44] HZ may as well occur in completely asymptomatic COVID-19 patients.[18]

HZ is reactivated when the host's cell-mediated immunity decreases. However, while the many studies propose that COVID-19 impairs T cell function, the intensity and interval of immunosuppression needed to trigger HZ is not yet known.[20]

The sequelae of the SARS-CoV-2 pandemic necessitated a speedy compilation of safe and effective prophylactic vaccines. Vaccination serves as the primary procedure for avoiding infections or lessening their severity through stimulating efficient cellular and humoral immunity reactions. DNA-based/RNA-based vaccines, non-replicating viral vector vaccines, and inactivated vaccines have been developed recently.[54] Topmost within these vaccines are the messenger RNA (mRNA) constructed vaccines, which are promising new technology against SARS-CoV-2 infection.[55] BNT162b2 became the first vaccine to be approved for emergency use. The vaccine showed 95% efficacy for protection against COVID-19 in a phase-II/III trial.[24]

The vaccination program In Kuwait against COVID 19 with BNT162b2 mRNA vaccine was launched in December 2020. Elderly people and the health care workers were prioritized in the beginning. Five immunocompetent cases of HZ after BNT162b2 mRNA vaccination, either after the first dose or after the second dose were monitored.

Common BNT162b2 mRNA vaccine-associated reported side effects include redness, and/or swelling at the injection site, pain, fatigue, headache, and fever.[24] Earlier reports acknowledged that vaccines can result in reactivation of HZV. Walter et al.[24] reported three cases of reactivation of HZV infections after vaccinations against other viruses such as inactivated influenza, hepatitis A, and rabies with Japanese encephalitis vaccines. One case developed HZ in the left T-10 dermatome 14 days after first dose of an inactivated hepatitis A vaccine. Another case was of a 80-year-old woman, who developed left thoracic HZ 6 days after receiving a dose of a trivalent influenza split-vaccine. Also, a 27-year-old white man, who had developed HZ in the second and third branches of the trigeminal nerve one day after receiving a vaccine against rabies and Japanese encephalitis viruses was discovered.[25] In the year 2000, 10 new cases of reactivated HSV infections soon after vaccination have been reported.[56] They involved five women and five men with an age range between 16 and 60. Moreover, Bayas et al.[57] reported a case of branchial plexus zoster after yellow fever vaccination.

Walter et al.[25] hypothesized that vaccination may trigger reactivation of herpes virus infections due to vaccine-induced immunomodulation, including suppression of cellular immunity by live attenuated vaccines and by inactivated hepatitis B vaccine. This may

be explained by the fact that both vaccination and reactivation of HZV infections are frequent, and a causal link is not suspected.[56]

Recent reports about reactivation of HZ after vaccination against COVID-19 have been published. Bostan et al.[58] reported a 78-year-old man who developed some crusted, hemorrhagic vesicles upon an erythematous base occupying an area corresponding to T3–T4 dermatomes 5 days after taking inactivated COVID-19 vaccine. Thus, inactivated COVID-19 vaccine has been implicated in the first reported case of reactivation of HZ.

The first case of HZ infection following mRNA vaccine for COVID-19, was a 79-year-old man, who presented with grouped vesicles on right thigh in a dermatomal distribution, noticed 6 days after receiving the vaccine. Systemic antiviral treatment was initiated resulting in the resolution of the condition.[59]

Furthermore, a 44-year-old healthcare provider displayed a herpetiform vesicular and erythematous rash on the left upper back and lateral and inner side of the left arm that followed C5–C6 dermatomes, 1 week after BNT162b2 mRNA COVID-19 vaccination. A clinical diagnosis of HZ was made. Post-zoster neuropathic pain lasted for a month.[60] The authors mentioned that immune dysregulation created by the vaccine played a role in the reactivation of latent HZV infection in their case.[60]

Psichogiou et al.[27] reported seven immunocompetent patients aged >50 years age, who had presented with HZ in a median of 9 days (range 7–20) after mRNA vaccination against SARS-CoV-2.

In contrast to our case series, Furer et al.[26] reported a six immunocompromised patients with autoimmune inflammatory diseases, who developed first episode of HZ closely after the first BNT162b2 mRNA vaccine; five developed HZ after the first dose and one after the second. The prevalence of HZ was 1.2% ($n = 6$) in patients with autoimmune inflammatory rheumatic diseases, compared with none in controls.[26]

The occurrence of HZ within the time window 1–21 days after vaccination defined for increased risk and the reported T cell-mediated immunity involvement suggest that COVID-19 vaccination is a probable cause of HZ.[27]

Català et al.,[61] classified cutaneous reactions after SARS-CoV-2 vaccination. From February 16 to May 15, 2021, they collected 405 reactions after vaccination with the BNT162b2 (Pfizer-BioNTech, 40.2%), mRNA-1273 (Moderna, 36.3%), and AZD1222 (AstraZeneca, 23.5%) vaccines. VZV reactivation was reported in 17.2% after BNT162b2, Pfizer-BioNTech vaccination.[61]

Potential mechanisms that might explain the pathogenetic link between mRNA-COVID19 vaccination and HZ reactivation are related to stimulation of innate immunity through toll-like receptors (TLRs) 3,7 by mRNA-based vaccines.[62]

Sahin U et al.[63] reported in healthy adults, vaccination with BNT162b2 induces a coordinated humoral and cellular adaptive immunity. Seven days after the booster dose, a strong cellular response with spike-specific CD8+ T cell and T helper type 1 (Th1) CD4+ T cells was expanding with a high fraction of them producing interferon-γ (IFNγ), a cytokine responsible for several antiviral responses.[63]

TLR signaling has been implicated during reactivation of herpesviruses, a process essential for these viruses to maintain themselves in the host.[64] Defects in TLR expression in patients suffering from diseases caused directly by herpes virus infection highlight the importance of these signaling pathways during infection and eventual disease progression.[64]

Thus, the vaccine stimulates induction of type I INFs and potent inflammatory cytokines, which instigate T and B immune responses, but may negatively affect antigen expression potentially contributing to HZ reactivation.[26]

These case reports support the importance of continuing assessment of vaccine safety during the ongoing massive vaccination for the COVID-19 pandemic and encourage reporting and communication of any vaccination-associated adverse event.[27]

5 | CONCLUSION

We have noted numerous case reports of HZ infection at the time of the current pandemic either in patients infected with COVID-19, even in patients with mild or no respiratory symptoms, and after COVID-19 vaccination. Experts must be aware of the probable increased hazard of HZ during the pandemic and propose appropriate curative and preventive steps against HZ infection. Correspondingly, we ought to consider that HZ infection may be accompanied by undetectable COVID-19. A systematic follow-up of these patients would be assumed to stick to extreme safety measures till the diagnosis of COVID-19 is omitted.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTION

All authors, namely Nawaf, Abdulrahman, Moneerah, and Sabika have contributed equally in carrying out the study as well as in preparation of the manuscript.

DATA AVAILABILITY STATEMENT

The data is available on request from the corresponding author, due to privacy/ethical restrictions.

REFERENCES

1. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*. 2020;7(1):4-26.
2. Heymann DL, Shindo N. WHO scientific and technical advisory Group for Infectious Hazards. COVID-19: what is next for public health? *Lancet*. 2020;395:542-545.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
4. Zhang YZ, Holes EC. A genomic perspective on the origin and emergence of sars-cov-2. *Cell*. 2020;181(2):223-227.
5. Wollina U, Karadağ AS, Rowland Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: a review. *Dermatol Ther*. 2020;33(5):e13549.

6. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. *J Dermatol Sci*. 2020;98(2):75-81.
7. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020; 12(1):1-5.
8. Kumar A, Arora A, Sharma P, et al. Clinical Features of COVID-19 and Factors Associated with Severe Clinical Course: A Systematic Review and Meta-Analysis 10.2139/ssrn.3566166
9. Wung PK, Holbrook JT, Hoffman GS, et al. Herpes zoster in immunocompromised patients: incidence, timing, and risk factors. *Am J Med*. 2005;118:1416.e18.
10. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44:1-26.
11. Tseng HF, Bruxvoort K, Ackerson B, Luo Y, et al. The epidemiology of herpes zoster in immunocompetent, unvaccinated adults ≥50 years old: incidence, complications, hospitalization, mortality, and recurrence. *J Infect Dis*. 2020;222:798-806.
12. Dayan RR, Peleg R. Herpes zoster-typical and atypical presentations. *Postgrad Med*. 2017;129(6):567-571.
13. Tartari F, Spadotto A, Zengarini C, et al. Herpes zoster in COVID-19-positive patients. *Int J Dermatol*. 2020;59(8):1028-1029.
14. Nofal A, Fawzy MM, Sharaf El Deen SM, El-Hawary EE. Herpes zoster ophthalmicus in COVID-19 patients. *Int J Dermatol*. 2020;59(12): 1545-1546.
15. Elsaie ML, Youssef EA, Nada HA. Herpes zoster might be an indicator for latent COVID 19 infection. *Dermatol Ther*. 2020;33(4):e13666.
16. Shors AR. Herpes zoster and severe acute herpetic neuralgia as a complication of COVID-19 infection. *JAAD Case Rep*. 2020;6(7): 656-657.
17. Ertugrul G, Aktas H. Herpes zoster cases increased during COVID-19 outbreak. Is it possible a relation? *J Dermatol Treat*. 2020;1:1180.
18. Ferreira A, Romão TT, Macedo YS, Pupe C, et al. COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy. *Eur J Neurol*. 2020;27(9):1748-1750.
19. 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;13:2361-2365.
20. Diez-Domingo J, Parikh R, Bhavsar AB, Cisneros E, McCormick N, Lecrenier N. Can COVID-19 increase the risk of herpes zoster? *Narrative Rev Dermatol Ther (Heidelb)*. 2021;11:1-8.
21. 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;13(1):e12423.
22. Saati A, Al-Husayni F, Malibari AA, et al. Herpes zoster co-infection in an immunocompetent patient with COVID-19. *Cureus*. 2020;12:e8998.
23. Elsaie ML, Youssef EA, Nada HA. Herpes zoster may be a marker for COVID-19 infection during pregnancy. *Cutis*. 2020;106:318-320.
24. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mMRNA COVID-19 vaccine. *N Engl J Med*. 2020;383: 2603-2615.
25. Walter R, Hartmann K, Fleisch F, Reinhart WH, Kuhn M. Reactivation of herpesvirus infections after vaccinations? *Lancet*. 1999;353:810.
26. Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. *Rheumatology (Oxford)*. 2021;60(SI):SI90-SI95.
27. Psichogiou M, Samarkos M, Mikos N, Hatzakis A. Reactivation of varicella zoster virus after vaccination for SARS-CoV-2. *Vaccines (Basel)*. 2021;9(6):572.
28. Waner JL. Mixed viral infections: detection and management. *Clin Microbiol Rev*. 1994;7(2):143-151.
29. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: current knowledge and future perspectives. *Dermatology*. 2021;237:1-12.
30. Singh H, Kaur H, Singh K, Sen CK. Cutaneous manifestations of COVID-19: a systematic review. *Adv Wound Care (New Rochelle)*. 2021;10(2):51-80.
31. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34:e212-e213.
32. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
33. Perna A, Passiatore M, Massaro A, et al. Skin manifestations in COVID-19 patients, state of the art. *Syst Rev Int J Dermatol*. 2021; 60(5):547-553.
34. 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;104:732-733.
35. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395: 497-506.
36. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients. *J Am Acad Dermatol*. 2020;83(1):280-285.
37. 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(3):e257-e259.
38. Packwood R, Galletta G, Tennyson J. An unusual case report of COVID-19 presenting with meningitis symptoms and shingles. *Clin Pract Cases Emerg Med*. 2020;4(3):316-320.
39. Ayaz CM, Dizman GT, Metan G, Alp A, Unal S. Out-patient management of patients with COVID-19 on home isolation. *Infez Med*. 2020; 28(3):351-356.
40. Pona A, Jiwani RA, Afriyie F, Labbe J, Cook PP, Mao Y. Herpes zoster as a potential complication of coronavirus disease 2019. *Dermatol Ther*. 2020;33(6):e13930.
41. Chan MH, Wong VW, Wong CK, et al. Serum LD1 isoenzyme and blood lymphocyte subsets as prognostic indicators for severe acute respiratory syndrome. *J Intern Med*. 2004;255(4):512-518.
42. Su R, Li Z, Wang Y, et al. Imbalance between Th17 and regulatory T cells in patients with systemic lupus erythematosus combined EBV/-CMV viraemia. *Clin Exp Rheumatol*. 2020;38(5):864-873.
43. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
44. Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol*. 2020;17: 533-535.
45. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846-884.
46. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58:1021-1028.
47. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province. *China Allergy*. 2020;75:1742-1752.
48. Liu WJ, Zhao M, Liu K. T-cell immunity of SARS-CoV: implications for vaccine development against MERS-CoV. *Antiviral Res*. 2017;137:82-92.
49. Drago F, Ciccarese G, Rebora A, Parodi A. Human herpesvirus-6, 7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol*. 2021;93(4):1850-1851.
50. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020; 12(1):8.

51. Xiao S, Luo D, Xiao Y. Survivors of COVID-19 are at high risk of post traumatic stress disorder. *Glob Health Res Policy*. 2020;5:29.
52. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39:405-407.
53. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunol Rev*. 2016;274:330-353.
54. Sharma O, Sultan AA, Ding H, Triggle CR. A review of the progress and challenges of developing a vaccine for COVID-19. *Front Immunol*. 2020;11:585354.
55. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med*. 2021;384:643-649.
56. Walter R, Hartmann K, Pool V, Gargiullo P, Kuhn M. Reaktivierung von herpesviren-infektionen durch impfungen: evidenz oder koinzidenz? (reactivation of herpes virus infections by vaccination: evidence or coincidence?). *Schweiz Med Wochenschr*. 2000;130(44):1685-1688.
57. Bayas JM, Gonzalez-Alvarez R, Guinovart C. Herpes zoster after yellow fever vaccination. *J Travel Med*. 2007;14:65-66.
58. Bostan E, Yalici-Armagan B. Herpes zoster following inactivated COVID-19 vaccine: a coexistence or coincidence? *J Cosmet Dermatol*. 2021;20(6):1566-1567.
59. Eid E, Abdullah L, Kurban M, Abbas O. Herpes zoster emergence following mRNA COVID-19 vaccine. *J Med Virol*. 2021;93(9):5231-5232.
60. Tessas I, Kluger N. Ipsilateral herpes zoster after the first dose of BNT162b2 mRNA COVID-19 vaccine. *J Eur Acad Dermatol Venereol*. 2021;35(10):e620-e622.
61. Català A, Muñoz-Santos C, Galván-Casas C, et al. Cutaneous reactions after SARS-COV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases. *Br J Dermatol*. 2021;186:142-152. doi:10.1111/bjd.20639
62. Zhang C, Maruggi G, Shan H, Li J. Advances in mRNA vaccines for infectious diseases. *Front Immunol*. 2019;10:594-599.
63. Sahin U, Muik A, Vogler I, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. *Nature*. 2021;595(7868):572-577.
64. West JA, Gregory SM, Damania B. Toll-like receptor sensing of human herpesvirus infection. *Front Cell Infect Microbiol*. 2012;8(2):122.

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