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Features of the course of primary and recurrent herpetic keratitis developing following COVID-19 vaccination

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Purpose: *To assess the features of the course of primary and recurrent herpetic keratitis (HK) developing following COVID-19 vaccination.*

Material and Methods: *Medical records of 31 patients (34 eyes) with post-COVID-19 vaccination HK were reviewed. The patients were divided into two post-COVID-19 vaccination HK groups: group 1 with primary HK (9 patients; 9 eyes) and group 2 with recurrent HK (22 patients; 25 eyes). Levels of total vitamin D, and immunoglobulin G (IgG) antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike receptor-binding domain (S-RBD), herpes simplex virus (HSV)-1/2, cytomegalovirus (CMV) and Epstein-Barr nuclear antigen (EBNA) were assessed in venous serum.*

Results: *The median time (interquartile range (IQR)) from COVID-19 vaccination to the development of keratitis was 15 days (10-30) for patients with primary HK and 7 days (4-10) for patients with recurrent HK. The level of vitamin D in venous serum was lower than normal in 84.2% of the total sample of patients. Of the eyes that developed primary HK following COVID-19 vaccination, 3 (33.3%) had dendritic HK and 6 (66.7%) had non-necrotizing stromal HK. Of the eyes that developed recurrent HK following COVID-19 vaccination, 2 (8%) had dendritic HK, 21 (81%) had non-necrotizing stromal HK and 2 (6%) had ulcerative necrotizing HK.*

Conclusion: *Non-necrotizing stromal HK was the most common form of post COVID-19 vaccination HK in both groups. The level of vitamin D in venous serum was lower than normal in 84.2% of post COVID-19 vaccination patients with HK. Levels of anti-HSV IgG, anti-EBNA IgG, anti-VZV IgG, and anti-CMV IgG antibodies in venous serum exceeded normal ranges in 86.5%, 96.4%, 92%, and 88.8%, respectively, of post COVID-19 vaccination patients with HK.*

Keywords:

COVID-19, herpetic keratitis, recurrent herpetic keratitis, herpes virus, cornea, vaccine

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced COVID-19 pandemic continues to spread all over the world [1]. Vaccination is an effective approach to reduce the burden of the current pandemic [1]. The results of clinical trials have proved the protective effect of vaccination against COVID-19 infection and transmission [2, 3]. The global pandemic required an unprecedented speed of vaccine development and approval. Millions of people received vaccines against COVID-19, but the vaccine safety data is limited.

Currently, there are four types of vaccine against COVID-19: the recombinant messenger RNA vaccines (Pfizer/BioNTech, BNT162b2 and Moderna, mRNA1273); protein subunit vaccines (Novavax); adenovirus vector-based vaccines (Oxford-AstraZeneca, ChAdOx1 nCoV-19 and Janssen Johnson & Johnson, Ad26.COV2.S), and inactivated virus vaccines (Sinovac, Sinopharm and Covaxin).

Wang et al [4], Haseeb et al [5], and Lee et al [6] described ocular (palpebral, orbital, corneal, ocular surface, retinal, choroidal and ocular motility) complications that can develop following COVID-19 vaccination.

The most common complications following COVID-19 vaccination are optic neuritis and uveitis, followed by ophthalmic herpes zoster, ischemic optic neuropathy [4, 7, 8, 9], and corneal transplant rejection [10, 11, 12].

Reactivation of herpes simplex virus (HSV) keratitis following COVID-19 vaccination has also been reported [12, 13].

Ophthalmic herpes is commonly caused by the HSV-1, and less commonly, by HSV-2. Ocular manifestations of HSV include blepharitis, conjunctivitis, corneal involvement and uveitis. Corneal lesions may cause loss of vision and may manifest clinically as epithelial or stromal herpetic keratitis (HK).

Recurrence of HK following vaccination has been documented following vaccination with the Zostavax, trivalent influenza, hepatitis A, and rabies vaccines. The United States Food and Drug Administration and World Health organization have acknowledged that the novel COVID-19 vaccines similarly have a risk of reactive immunologic-based inflammation, namely, myositis, pericarditis, and Guillain-Barré syndrome [14].

History of stromal keratitis is a major risk factor for recurrent HK. Age, sex, ethnicity and previous history of non-ocular HSV disease were not associated with an increased risk of recurrence [15]. Herpes zoster virus (HZV) may cause ophthalmic herpes manifested by cutaneous rash, conjunctivitis, keratitis and uveitis [16].

Therefore, cases and case series of HK reactivation following vaccination with a recombinant or adenovirus vector-based vaccine have been reported, but it has not been sufficiently explored how this was associated with patient's general health status.

The purpose of this study was to assess the features of the course of primary and recurrent HK developing following COVID-19 vaccination.

Material and Methods

Patients treated for post-COVID-19 vaccination HK on an in-patient basis at the Division of Corneal Microsurgery, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", were included in the study. Medical records of 31 patients (34 eyes) with post-COVID-19 vaccination HK were reviewed. The patients were divided into two groups: group 1 with primary HK (9 patients; 9 eyes) and group 2 with recurrent HK (22 patients; 25 eyes). The mean age in both groups was 53 years (standard deviation (SD) 16.3). The two groups included 15 males (48.4%) and 16 females (51.6%). Exclusion criteria were patients with diabetes mellitus, autoimmune diseases or immunosuppressive conditions.

This study was approved by the Ethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (committee meeting minutes of November 5, 2024) and informed consent was obtained from all study subjects.

One patient with primary HK following COVID-19 vaccination had a 12-month history of keratoplasty for corneal endothelial and epithelial degeneration, and presented with evidence of graft rejection in the form of stromal keratitis.

Medical records indicated that, of the study patients, 19, 11, 8, 2 and 1 received the CoronaVac, Pfizer, Sinovac and Moderna vaccines, respectively.

With regard to the clinical form, corneal lesions of HK were defined as those of epithelial dendritic HK, non-necrotizing stromal HK and ulcerative necrotizing HK, as per classification by Liesegang [17].

The levels of immunoglobulin G (IgG) antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike receptor-binding domain (S-RBD) in venous serum were measured for evidence of immune response after COVID-19 vaccination.

Sample values of 40-50 AU/ml were classified as borderline, and values of > 50AU/ml, positive for anti-SARS-CoV-2 IgG antibodies.

Levels of IgG antibodies against HSV1 and 2 and cytomegalovirus (CMV) were measured with an automatic enzyme immunoassay (Lazurite, Dynex Technologies Ltd, USA). Levels of IgG antibodies against Epstein-Barr nuclear antigen (EBNA) and Varicella zoster virus (VZV) were measured with an immunoassay system (IMMULITE 2000, Siemens Healthcare Diagnostics Inc., USA). Sample values of ≥1.1 were classified as positive for anti-HSV1 and anti-HSV2 IgG, anti-CMV IgG, anti-EBNA IgG and anti-VZV IgG antibodies. Venous serum levels of total vitamin D [25(OH) D3 plus 25(OH) D2] were measured with a Mindray CL-6000i automatic chemiluminescence immunoanalyzer (Shenzhen Mindray Biomedical Electronics Co., Ltd. Shenzhen, China). Total vitamin D levels of 10–30 ng/mL were classified as insufficient, and 30–100 ng/mL were classified as normal. Soluble fibrin monomer complex (SFMC) levels of 3.38-4.5 milligram percent (mg%) in venous serum were classified as normal.

Statistics

IBM SPSS Statistics software version 26 (IBM Corp., Armonk, NY) was used for the statistical analysis. The data obtained were entered into a spreadsheet database. Nominal data were described using numbers with percentages. Smirnov test or Shapiro-Wilk tests were performed to determine normality of data. The Student t test was used to compare mean values of normally distributed numerical variables. Non-normally distributed data were described using median and interquartile range (IQR) and compared using the Mann–Whitney U test. The Pearson chi-square test was applied for comparison of nominal data. Yates-corrected chi-square test was applied if the expected frequency was less than 10 in at least one cell for four-field tables.

Results

In the group with primary HK developing following COVID-19 infection, all 9 patients (9 eyes) had unilateral ocular lesions. In the group with recurrent HK developing following COVID-19 vaccination, 19 patients had unilateral ocular lesions and 3 patients had bilateral ocular lesions.

The median time (IQR) from COVID-19 vaccination to the development of keratitis was 15 days (10-30) for patients with primary HK and 7 days (4-10) for patients with recurrent HK. In group 1, 5 patients (55.6%) developed primary HK following the first vaccine dose, and 4 patients (44.4%) developed primary HK following the second vaccine dose. In group 2, 10 patients (40%) developed recurrent HK following the first vaccine dose and 11 patients (44%) developed recurrent HK following the second vaccine dose. In addition, 4 patients had a COVID-19 vaccine dose despite noted symptoms of ocular inflammation (redness, discomfort and tearing), which resulted in significantly worsened ocular symptoms and required visiting an ophthalmologist. We believed it was feasible to include the latter patients in the study because it was the vaccination that triggered the development of an apparent clinical picture of HK (Table 1).

There was no statistical difference between groups in the rate of the development of primary or recurrent keratitis following COVID-19 vaccination or the number of received vaccine doses.

Of the eyes that developed primary HK following COVID-19 vaccination, 3 (33.3%) had dendritic HK and 6 (66.7%) had non-necrotizing stromal HK (Table 2). Of the eyes that developed recurrent HK following COVID-19 vaccination, 2 (8%) had dendritic HK, 21 (81%) had non-necrotizing stromal HK and 2 (6%) had ulcerative necrotizing HK (Table 2).

Therefore, non-necrotizing stromal HK was more common in eyes with recurrent HK than in eyes with primary HK (84% vs 62.5%, respectively) and was the most common form of post COVID-19 vaccination HK in both groups. Of the eyes with primary HK, 37.5% had dendritic HK, and no eye had ulcerative necrotizing HK. Of the eyes with recurrent HK that developed following COVID-19 vaccination, 8% had dendritic HK, and 8% had ulcerative necrotizing HK.

The level of vitamin D in venous serum was lower than normal in 84.2% of the total sample of patients, and the mean venous serum level of vitamin D for the total sample of patients was 24.4 ± 8.5 ng/ml.

The venous serum level of IgG antibodies against HSV-1 or HSV-2 was higher than normal in 86.5% of patients, and the mean venous serum level of IgG antibodies against HSV-1 or HSV-2 for the total sample of patients was 36.5 ± 16.0 ng/ml.

Levels of anti-EBNA IgG, anti-VZV IgG, and anti-CMV IgG in venous serum exceeded normal ranges in 96.4%, 92%, and 88.8%, respectively, of the examined patients. The venous serum level of IgG antibodies against the SARS-CoV-2 S-RBD was higher than normal in all patients in both groups.

The level of SFMC in venous serum was by 14.2% and significantly ($p = 0.038$) higher in patients that developed recurrent HK than in patients that developed primary HK following COVID-19 vaccination, but was within the reference range (Table 3).

Table 1. Number of cases of primary or recurrent herpetic keratitis that developed after COVID-19 vaccination

Herpetic keratitis	After the first vaccination	After the second vaccination	Vaccination in the presence of recurrent HK
Primary HK (n = 9)	5	4	-
Recurrent HK (n = 25)	10	11	4

Note: HK, herpetic keratitis; n, number of eyes

Table 2. Incidence of the clinical forms of herpetic keratitis that developed following COVID-19 vaccination

Group	Dendritic keratitis	Non-necrotizing stromal keratitis	Ulcerative necrotizing keratitis
	1	2	3
	n (%)	n (%)	n
Primary HK that developed following COVID-19 vaccination	3 (33.3%)	6 (66.6%)	-
	Totally, 9 eyes (100%)		
Recurrent HK that developed following COVID-19 vaccination	2 (8%)	21 (84%)	2 (8%)
	Totally, 25 eyes (100%)		

Note: HK, herpetic keratitis; n, number of eyes

Table 3. Level of soluble fibrin monomer complexes (SFMC) in venous serum in patients with herpetic keratitis that developed following COVID-19 vaccination

Group	SFMC, mg%	P-value
	M ± SD	
Primary herpetic keratitis that developed following COVID-19 vaccination	3.5 ± 0.4	P = 0.038
Secondary herpetic keratitis that developed following COVID-19 vaccination	4.0 ± 0,5	

Note: M, mean value; SD, standard deviation

Discussion

Keratitis is a rare adverse effect of vaccination. Grillo and Fraunfelder [18] identified 24 cases of keratitis after receiving a live attenuated VZV vaccine. Vaccinations against non-herpes virus, especially influenza vaccinations, have the risk of leading to the reactivation of ocular herpes virus infection. Rothova and colleagues [19] reported a recurrence of VZV-related acute retinal necrosis in a patient following vaccination against flu H1N1.

The exact mechanisms that trigger the reactivation of ocular herpes virus infection following inactivated vaccination against COVID-19 are not clearly understood. Neurotropic HSV and VZV establish a latent infection for the entire life of the host, and their reactivations have been attributed to insufficient cellular immunity [20]. Vaccine-induced immunomodulation (e.g., immunosuppressive effect, decreased alloreactivity) had been previously documented in the literature [21, 23]. Therefore, a temporary decrease of cell-mediated immunity during the early period post vaccination may be involved. Other proposed mechanisms include molecular mimicry, in which host proteins are mimicked by those within the vaccine, thus triggering a host response [13]. A further proposed mechanism includes autoinflammation triggered by the vaccine, with possible reduction in neurotrophin allowing HSV replication. In addition, distraction of humoral response due to vaccination may lead to loss of immunological control of HSV [23].

The reports on adverse effects in various organs and systems (including the visual system) have begun to appear after the wide application of COVID-19 vaccines [24]. Song and colleagues [25] reported on a 30-year-old female patient that developed disciform HK 7 days following the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine. Richardson-May and colleagues [13] reported that an 82-year-old man with a history of herpes simplex keratitis 40 years previously, showed reactivation of herpes simplex keratitis following the viral vector vaccine (Oxford/AstraZeneca COVID-19 vaccine) for COVID-19. Alkwikbi and colleagues [26] presented four cases of HSV reactivation and endothelitis in patients who received COVID-19 vaccination in Saudi Arabia from different medical centers. Papasavvas and colleagues [27] reported that herpes zoster ophthalmicus was found in one patient 16 days after a single booster dose of vaccination (Pfizer BioNTech) and in two patients, 10 days after the first dose of Pfizer BioNTech COVID-19 vaccine and 16 days after the first dose of the Moderna COVID-19 vaccine, respectively.

The COVID-19 vaccines, however, have over 90% efficacy in preventing a disease that was responsible for about 2.6 million deaths worldwide during its first year alone; this medical advancement provides paramount protection to both the individual and society at large [28]. For patients with HSV and VZV with history of ocular involvement, clinicians may wish to observe for ocular changes presenting around the time for vaccination. Patients may also be advised to self-monitor vision and ocular symptoms in the weeks following vaccinations and to report any changes immediately.

Our findings confirm that COVID-19 vaccination with the Pfizer, CoronaVac, Sinovac, Astra Zeneca, or Moderna vaccine can trigger herpes virus activation or reactivation with the development of primary or recurrent HK.

Hospitalized patients with COVID-19 infection frequently have coagulopathy resembling disseminated intravascular coagulation [29].

The role of fibrin degradation products (e.g., SFMC) in the course of HK developing following COVID-19 is still to be determined. In the current study, the level of SFMC in venous serum was by 14.2% and significantly ($p = 0.038$) higher in patients that developed recurrent HK than in patients that developed primary HK following COVID-19 vaccination, but was within the reference range.

A deficiency in vitamin D is a factor associated with worse sequelae and the severity and number of complications of respiratory infections. Vitamin D has immunomodulating effects on innate and adaptive immune responses. It has been shown to play a role in reducing cytokine storm and stimulate production of antimicrobial proteins which can lower viral replication rate. Recent studies demonstrated an association of vitamin D deficiency with COVID-19 infection severity and mortality [30, 31].

Of note that, in the current study, the level of vitamin D in venous serum was lower than normal in 84.2% of post COVID-19 vaccination patients. To our knowledge, no similar findings have been reported in the literature.

Conclusion

Non-necrotizing stromal HK was more common in eyes with recurrent HK than in eyes with primary HK (84% vs 62.5%, respectively) and was the most common form of post COVID-19 vaccination HK in both groups.

The level of vitamin D in venous serum was lower than normal in 84.2% of post COVID-19 vaccination patients with HK. Levels of anti-HSV IgG, anti-EBNA IgG, anti-VZV IgG, and anti-CMV IgG antibodies in venous serum exceeded normal ranges in 86,5%, 96.4%, 92%, and 88.8%, respectively, of post COVID-19 vaccination patients with HK. Given our findings on the development of primary and recurrent HK in post COVID-19 vaccination patients, we advise individuals with a history of HK to have a preventive course of antiviral therapy before and after COVID-19 vaccination, and to avoid vaccination in the presence of signs of ocular inflammation.

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Disclosures

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Abbreviations: *CMV, cytomegalovirus; HK, herpetic keratitis; HSV, herpes simplex virus; MV, mechanical ventilation; SFMC, soluble fibrin monomer complexes; VZV, varicella zoster virus*