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Features of the course of post-COVID-19 primary and recurrent herpetic keratitis

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

Material and Methods: *Medical records of 70 patients (83 eyes) with post-COVID-19 HK were reviewed. The patients were divided into two groups: group 1 with primary HK (26 patients; 30 eyes) and group 2 with recurrent HK (44 patients; 53 eyes). COVID-19 severity was defined as mild (without evidence of viral pneumonia), moderate (pneumonia not treated at the intensive care unit (ICU)) and severe (treatment at the ICU). Levels of total vitamin D, and immunoglobulin G (IgG) against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, herpes simplex virus (HSV)-1/2, cytomegalovirus (CMV) and Epstein-Barr nuclear antigen (EBNA) in venous blood were assessed.*

Results: *Dendritic HK and ulcerative necrotizing HK were more common in patients with primary keratitis than in recurrent keratitis (20.7% vs 2% and 41.2% vs 15.6%, respectively). Non-necrotizing stromal HK was more common in the latter patients than in the former patients (82.4% vs 37.9%, respectively) and was the most common form of post-COVID-19 HK in both groups. Ulcerative necrotizing HK was more common in patients with primary HK than in patients with recurrent HK (41.4% vs 15.6%, respectively) and was mainly observed after severe COVID-19. In patients with ulcerative necrotizing HK, the level of HSV IgG was 1.6 times higher than in patients with epithelial HK, and 1.5 times higher than in patients with non-necrotizing stromal HK. Elevated anti-VZV, anti-EBNA, and anti-CMV IgG levels were found in 93.2%, 76.4%, and 86.4%, respectively, of the examined patients.*

Conclusion: *SARS CoV 2 infection may be a potential risk factor for HSV reactivation from latency and primary or recurrent HK, with an increase in the frequency of bilateral ocular lesions and stromal forms of HK. The ophthalmologist must be aware of this ocular complication in COVID 19–infected cases, which may present either during acute or recovery phase of the illness; it mostly occurs in severely infected patients.*

Keywords:

COVID 19, herpetic keratitis, recurrent herpetic keratitis, herpes simplex virus, cornea

Introduction

The SARS-COV-2-induced COVID-19 pandemic has affected hundreds of millions of people and over 200 countries, and posed an unprecedented challenge to global health [1]. An increase in COVID-19 prevalence, limitations to movement of people and lack of the possibility to receive required medical care led to an increase in the pathology requiring urgent care and exacerbation of chronic somatic and eye pathology.

Herpetic keratitis (HK) is one of the most common corneal infections [2]. Herpes simplex virus (HSV) establishes latency in the neural ganglion after primary infection in the body (after primary ocular HSV infection, the virus establishes latency most commonly in the trigeminal ganglia) [3]. HSV reactivation from latency may be triggered by exposure to cold or ultraviolet light; emotional, psychic or temperature stress; systemic infections, or trauma. In addition, other viral disorders (including COVID-19) may trigger HSV reactivation. COVID-19 is known to be a contributor to exacerbation of chronic inflammatory diseases like HK. In primary HK, the damage is generally limited to the surface epithelium, whereas in recurrent HK, the damage often (20-50%) extends to the stroma and endothelium.

Herpetic stromal keratitis (HSK) is one of the most common recurrent ocular infections and a leading cause of unilateral infectious corneal blindness.

Ocular manifestations reported in COVID-19 patients include conjunctivitis, anterior uveitis, sclerouveitis, reactivation of inactive anterior uveitis, vitritis, panuveitis, retinal hemorrhage, retinal artery or vein occlusion, multifocal chorioretinitis, and central serous chorioretinopathy [4-10]. There were isolated reports of HSV or Herpes Zoster keratitis in patients after COVID-19 infection [11-13].

However, no study including the analysis of numerous cases of post-COVID-19 HK has been conducted, and the features of the course of HK as a sequela of COVID-19 infection have not been studied yet.

The purpose of the study was to assess the features of the course of post-COVID-19 primary and recurrent HK.

Material and Methods

The study was conducted at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine". Medical records of 70 patients (83 eyes) with post-COVID-19 herpetic keratitis were reviewed. The patients were divided into two groups: group 1 with post-COVID-19 primary herpetic keratitis (26 patients; 30 eyes) and group 2 with post-COVID-19 recurrent herpetic keratitis (44 patients; 53 eyes). The mean age in both groups was 55 years (SD 14.8). The two groups included 37 males (52.8%) and 33 females (47.2%). Group 1 included 22 patients with unilateral ocular lesions (22 eyes) and four patients with bilateral ocular lesions (8 eyes). Group 2 included 35 patients with unilateral ocular lesions (35 eyes) and nine patients with bilateral ocular lesions (18 eyes). The two groups included 57 eyes (68.7%) with unilateral lesions and 26 eyes (31.3%) with bilateral lesions. Herpetic keratitis patients with a history of COVID-19 confirmed by the report provided by the in-patient pulmonary department team, medical history, positive polymerase chain reaction test and SARS-CoV-2 express test were included in the study. 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 July 9, 2024) and informed consent was obtained from all study subjects.

Three patients with a history of keratoplasty (one case each for corneal dystrophy, keratokonus, and recurrent HK) developed post-COVID-19 HK in the form of graft disease. These patients were excluded from this analysis and will be reported separately.

COVID-19 severity was defined as mild (without evidence of viral pneumonia), moderate (clinical signs of pneumonia) and severe (clinical signs of pneumonia and treatment at the intensive care unit) [14]. 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. Patient groups were formed according to Liesegang's classification [15].

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 blood were measured to confirm a history of COVID-19 infection. 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 blood 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 blood were classified as normal.

Statistical analysis

Statistical analyses were conducted using Statistica 8.0 (StatSoft, Tulsa, OK, USA) software. The data obtained were entered into a spreadsheet database. Nominal data were described using numbers with percentages. The Kolmogorov-Smirnov test or Shapiro-Wilk tests were performed to determine normality of data. Mean and SD values were calculated for normally distributed data. The Student t test was used to compare mean values of normally distributed numerical variables. Non-normally distributed data were described using median (Med) and interquartile range (IQR) and compared using the Mann–Whitney U test. Odds Ratio (OR) was used as a quantitative measure of effect for the comparison of relative characteristics. The 95% CI was calculated to project the OR values for the population. 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

With regard to primary HK developing after COVID-19, 22 patients (22 eyes; 73.4%) had unilateral HK, and 4 patients (8 eyes; 26.6%) had bilateral HK. With regard to recurrent HK developing after COVID-19, 35 patients (35 eyes; 66%) had unilateral HK, and 9 patients (18 eyes; 34%) had bilateral HK.

Of the eyes with primary HK, 6 (20.7%) had dendritic HK, 11 (37.9%) had non-necrotizing stromal HK and 12

(41.4%) had ulcerative necrotizing HK. Of the eyes with recurrent HK, one (2.0%) had dendritic HK, 42 (82.4%) had non-necrotizing stromal HK and 8 (15.6%) had ulcerative necrotizing HK (Table 1).

Therefore, dendritic HK was more common in eyes with primary HK than in eyes with recurrent HK (χ^2=6.5 (p=0.02)). Dendritic HK was more likely to develop in eyes with primary HK than in eyes with recurrent HK (OR, 19.0; 95% CI, 2.3-157.0).

Non-necrotizing stromal HK was more frequently seen in patients with recurrent HK than in patients with primary HK (χ^2 = 14.3; p = 0.0001; Table 1).

Ulcerative necrotizing HK occurred significantly more frequently in patients with primary HK than in patients with recurrent HK (χ^2 = 5.2; p = 0.02). Corneal ulcer was 3.9 times more likely to occur in primary keratitis than in recurrent HK (OR, 3.93; 95% CI, 1.5-10.5).

The time from the diagnosis of COVID-19 to the development of keratitis ranged from 0 to 90 days (median (IQR), 9 (0 - 15) days) for patients with primary HK, and ranged from 0 to 720 days (median (IQR), 10 (0 - 22) days) for patients with recurrent HK.

Of the patients with primary HK, 13 (33.8%) had mild COVID-19, 8 (27.6%) had moderate COVID-19, and 8 (27.6%) had severe COVID-19. Of the patients with recurrent HK, 34 (66.7%) had mild COVID-19, 9 (17.7%) had moderate COVID-19, and 8 (15.6%) had severe COVID-19.

Ulcerative necrotizing HK occurred significantly more frequently after severe COVID-19 than after mild COVID-19 (χ^2 = 6.3, P = 0.01, Table 2).

Corneal ulcer was 5.7 times more likely to occur in patients after severe COVID-19 than after mild COVID-19 (OR, 5.7; 95% CI, 1.6-20.3).

Blood S-protein IgG level ranged from 259 to 17061 AU/ml (median (IQR), 1972 (940-6925)) in patients with primary HK, and from 37 to 80000 AU/ml (median (IQR), 2139 (769-3931)) in patients with recurrent HK (Table 3).

Table 3 shows that, among patients with post-COVID-19 HK, blood S-protein IgG level was highest in patients with stromal keratitis, and this difference was significant (P2-3 = 0.01). In addition, the blood S-protein IgG level exceeded the normal range in 88.9% of the examined patients. In a total sample of patients with post-COVID-19 HK, the mean SFMC level was 4.22 ± 0.7 mg%. Mean SFMC level was 4.2 ± 0.5 mg% in patients with primary HK, and 4.2 ± 0.8 mg% in patients with recurrent HK, with no significant difference between groups.

Mean total vitamin D level was 28.9 ± 9.2 ng/ml for patients with dendritic HK, 22.7 ± 8.0 ng/ml for patients with non-necrotizing stromal HK, and 24.5 ± 13.0 ng/ml for patients with corneal ulcer, of a total sample of patients with post-COVID-19 HK (Table 4). Table 4 shows that, although there was a difference in patient number between the total sample of patients with dendritic HK and the total

Table 1. Frequency of clinical forms of herpetic keratitis in post-COVID-19 patients

Group	Dendritic keratitis	Non-necrotizing stromal keratitis	Ulcerative necrotizing keratitis
	n (%)	n (%)	n (%)
Post-COVID-19 primary herpetic keratitis	6 (20.7%)	11 (37.9%)	12 (41.4%)
	29 (100%)		
Post-COVID-19 recurrent herpetic keratitis	1 (2.0%)	42 (82.4%)	8 (15.6%)
	51 (100%)		

Note: n (%), number (percentage) of eyes

Table 2. Frequency of corneal ulcer in post-COVID-19 patients with different COVID-19 severity

Presence or absence of corneal ulcer	Mild COVID-19 (47 eyes)	Moderate COVID-19 (eyes)	Severe COVID-19 (16 eyes)
	1	2	3
Presence of corneal ulcer	7 (14.9%)	4 (25%)	8 (50%)
Absence of corneal ulcer	40 (85.1%)	12 (75%)	8 (50%)

Note: 1, 2, and 3 are indices assigned to COVID-19 severity stages for the calculation of p

Table 3. Levels of SARS-CoV-2 IgG in venous blood (AU/ml) in patients with different forms of post-COVID-19 herpetic keratitis

Group	Levels of SARS-CoV-2 IgG in venous blood (AU/ml)		
	Dendritic keratitis	**Non-necrotizing stromal keratitis**	**Ulcerative necrotizing keratitis**
	Median Q_1-Q_3	Median Q_1-Q_3	Median Q_1-Q_3
	1	2	3
Primary herpetic keratitis	940 0 –1347 n = 3	1972 1546 – 10594 n = 11	940 0-5169 n = 7
	–		
Recurrent herpetic keratitis	– n = 1	2720 1295 – 4355 n = 28	484 302 – 643 n = 4
	P_{2-3} = 0.01		

Note: IgG, immunoglobulin G; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-RBD, spike receptor-binding domain

Table 4. Levels of vitamin D in venous blood (ng/ml) in patients with different forms of post-COVID-19 herpetic keratitis

Nosological form	Levels of vitamin D in venous blood (ng/ml)		
	Dendritic keratitis	**Non-necrotizing stromal keratitis**	**Ulcerative necrotizing keratitis**
	M±SD	M±SD	M±SD
	1	2	3
Primary or recurrent herpetic keratitis	28.9±9.2 n=5	22.7±8.0 n=53	24.5±13.0 n=11
	P_{1-2} = 0.05		

Note: M, mean value; SD, standard deviation; 1, 2, and 3 are indices assigned to COVID-19 severity stages for the calculation of p

Table 5. Levels of HSV IgG in venous blood (ng/ml) in patients with different forms of post-COVID-19 herpetic keratitis

Group	Levels of HSV IgG in venous blood (ng/ml)			
	Dendritic keratitis	**Non-necrotizing stromal keratitis**	**Ulcerative necrotizing keratitis**	**P**
	M±SD n=6	M±SD n=53	M±SD n=14	
	1	2	3	
HSV 1/2	32.8±21.1	33.2±16.7	51.3±20.3	P_{1-3}=0.04 P_{2-3}=0.009

Note: HSV, herpes simplex virus; M, mean value; SD, standard deviation; 1, 2, and 3 are indices assigned to COVID-19 severity stages for the calculation of p

sample of patients with non-necrotizing stromal HK, the level of vitamin D in venous blood was 27.3% higher in the former patients than in the latter patients ($p = 0.05$). It is noteworthy that total vitamin D level in venous blood was within the normal range only in 12.5% of the examined patients.

Table 5 shows the distribution of blood HSV IgG and demonstrates that the concentration of HSV IgG in venous blood was significantly higher in patients with ulcerative necrotizing HK (51.3 ± 20.3 ng/ml) than in patients with dendritic HK (32.8 ± 21.1 ng/ml, $p = 0.04$) and in patients with non-necrotizing stromal HK (33.2 ± 16.7 ng/ml, $p = 0.009$). Mean level of anti-EBNA IgG in venous blood was 9.4 ± 7.3 ng/ml for patients with dendritic HK, 12.06 ± 6.0 ng/ml for patients with non-necrotizing stromal HK, and 10.09 ± 6.0 ng/ml for patients with ulcerative necrotizing HK of both groups. Mean level of anti-VZV IgG in venous blood was 9.4 ± 4.6 ng/ml for patients with dendritic HK, 8.6 ± 3.1 ng/ml for patients with non-necrotizing stromal HK, and 7.6 ± 4.2 ng/ml for patients with ulcerative necrotizing HK of both groups.

Mean level of anti-CMV IgG in venous blood was 15.9 ± 11.5 ng/ml for patients with dendritic HK, 13.1 ± 8.2 ng/ml for patients with non-necrotizing stromal HK, and 15.1 ± 7.7 ng/ml for patients with ulcerative necrotizing HK of both groups. The level of anti-CMV IgG in venous blood exceeded the normal range in 86.4% of the examined patients.

There was no significant difference in the level of anti-EBNA IgG, anti-VZV IgG, or anti-CMV IgG in venous blood between the groups. Levels of anti-VZV IgG and anti-EBNA IgG in venous blood exceeded normal ranges in 93.2% and 76.4%, respectively, of the examined patients.

Discussion

HSV-1 belongs to the human herpes virus alpha subfamily, which is a neurotropic virus and establishes latency in the neural ganglion after primary infection in the body. The eye is the second (after the oral cavity) most common initial site of HSV-1 infection. The most common ocular manifestation of HSV is keratitis, but the virus may also cause conjunctivitis, uveitis or acute retinal necrosis. Triggering factors for HSV-1 reactivation are supposed to be psychological stress, trauma, fever, weakening of the immune system, and the presence of inflammatory mediators such as cytokines [16].

It has been supposed that COVID-19 may trigger the development of HK [17].

Diagnosing HSV typically involves identifying the virus or its proteins, HSV-specific antibodies, or HSV genetic materials in the blood [18].

There have been several case reports of reactivation of latent viral infections, including HSV infections, among COVID 19 patients [19]. In a study by Seeßle and colleagues [20], a high rate of HSV-1 reactivation (83.3%, 15 out of 18 patients) was found in COVID-19 patients on invasive ventilation, after median 9 days of ventilation. Bilateral conjunctivitis, an ophthalmic HSV infection, was reported in a 69-year-old Caucasian male with moderate COVID 19 disease [21]. Majtanova and colleagues [22] reported five cases of HSV-1 keratitis (two of which were bilateral) in COVID-19 patients. In addition, they reported that, during the second pandemic wave in Slovakia (September 2020–January 2021), a 2.5- and 2-fold higher incidence of herpes keratitis was observed in their department of ophthalmology in comparison to the same period in 2019 and 2018, respectively.

All cases of HK following COVID-19 reported in the literature are of isolated nature; to the best of our knowledge, no study with an analysis of numerous patients with post-COVID-19 HK has been conducted.

Ocular HSV is most often a unilateral disease, but bilateral disease has been reported in 2–19% of cases [23]. The incidence of bilateral HSV keratitis has been reported to be especially high in children (up to 26%) and patients with immunosuppression or other comorbidities (e.g., up to 40% in rheumatoid arthritis patients) [24]. Bilateral HSV keratitis has been reported for patients with congenital immune deficiencies, atopy, autoimmune diseases, ocular rosacea, longterm immunosuppression, corticosteroid use and organ transplantation [24].

A bilateral lesion indicates a greater inflammation area than a monolateral lesion; in the current study, bilateral HK lesions were seen in 26.6% of the affected eyes with primary HK following COVID-19 infection, and 34% of the affected eyes with recurrent HK following COVID-19 infection.

HSV infection can be demonstrated by the presence of IgG antibodies in serum, whereas the identification of IgM and higher IgG antibody levels indicate more frequent HSV reactivation [25].

We found that, in patients with ulcerative necrotizing HK, the level of IgG antibodies against HSV-1/2 in venous blood was 1.6 times higher than in patients with epithelial HK, and 1.5 times higher than in patients with non-necrotizing stromal HK. It may be hypothesized that, in patients with ulcerative necrotizing HK, the body (and particularly the ocular tissue) is more severely affected by the virus and its products, and the immune response is more active, than in patients with dendritic HK or non-necrotizing stromal HK.

A retrospective study of hospitalized COVID-19 patients in Wuhan, China during early 2020 found EBV reactivation in 55 of 217 patients [26]. EBV viremia at the time of COVID-19 diagnosis was one of the four factors for long COVID development [27].

In the present study, there was no significant difference in the level of anti-EBNA IgG, anti-VZV IgG, or anti-CMV IgG in venous blood between the groups. In addition, elevated anti-VZV IgG, anti-EBNA IgG, and anti-CMV IgG levels in venous blood were found in 93.2%, 76.4%, and 86.4% of the examined patients.

Hospitalized patients with COVID-19 infections frequently have coagulopathy resembling disseminated intravascular coagulation (DIC) [28]. An elevation

of D-dimer level is associated with a poor prognosis; however, the role of other fibrin degradation products, such as SFMC, is not known [28].

We found that, in patients with HK following COVID-19 infection, SFMC in venous blood were at the upper end of the normal range, with no significant difference between the groups of patients with primary HK and patients with recurrent HK.

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 an immunomodulating effect on congenital and adaptive immune response. 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 [29, 30].

It is noteworthy that, in the current study, vitamin D level in venous blood was within the normal range only in 12.5% of the examined patients. In addition, the level of vitamin D in venous blood was 27.3% higher in patients with dendritic HK than in patients with non-necrotizing stromal HK ($p = 0.05$). To our knowledge, no similar findings have been reported in the literature.

One of the important things to remember is that as majority of the critical care patients will not be able to communicate their visual problems, intensive care unit personnel should be vigilant in identifying patients with evolving ophthalmic signs for further assessment and should promptly refer them to an ophthalmologist, as this keratitis may be blinding if not addressed timely and properly [31].

In conclusion, SARS CoV 2 infection may be a potential risk factor for developing HSV 1 keratitis, and the ophthalmologist must be aware of this ocular complication in COVID 19–infected cases, which may present either during acute or recovery phase of the illness; it mostly occurs in severely infected patients.

Therefore, we established the differences in the frequency of clinical forms between primary and recurrent HK developing after COVID-19 infection: dendritic HK and ulcerative necrotizing HK were more common in primary keratitis than in recurrent keratitis (20.7% vs 2% and 41.2% vs 15.6%, respectively). Corneal ulcer was 3.9 times more likely to occur in primary keratitis than in recurrent HK (OR, 3.93; 95% CI, 1.5-10.5). Non-necrotizing stromal HK was more common in patients with recurrent HK than in patients with primary HK (82.4% vs 37.9%, respectively) and was the most common form of post-COVID-19 HK in both groups. Ulcerative necrotizing HK was mainly observed after severe COVID-19 infection. Corneal ulcer was 5.7 times more likely to occur in patients after severe COVID-19 than after mild or moderate COVID-19.

In patients with ulcerative necrotizing HK, the level of IgG against HSV-1 or HSV-2 in venous blood was 1.6 times higher than in patients with epithelial HK, and 1.5 times higher than in patients with non-necrotizing stromal HK. Levels of anti-VZV IgG, anti-EBNA IgG and anti-CMV IgG in venous blood exceeded normal ranges in 93.2%, 76.4%, and 86.4%, respectively, of the examined patients.

Vitamin D level in venous blood was within the normal range only in 12.5% of the examined patients. The level of vitamin D in venous blood was 27.3% higher in patients with dendritic HK than in patients with non-necrotizing stromal HK ($p = 0.05$).

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