• Brief Report •

COVID-19 infection with keratitis as the first clinical manifestation

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Abstract

● **AIM:** To report a case which keratitis is the first clinical manifestation of COVID-19 that occurred 3d earlier than the common COVID-19 symptoms.

● **METHODS:** Regular slit lamp examination, corneal scraping test, and chest computed tomography (CT) were performed for patients with COVID-19 infection. The ophthalmologic treatment included ganciclovir eye drop (50 mg/mL, 6 times/d). The treatment for diarrhea included Guifu Lizhong pills (TID). The antiviral therapy consisted of oseltamivir (75 mg capsule Q12H); therapy preventing bacterial infection consisted of azithromycin (250 mg tablet QD) and moxifloxacin (0.4 g tablet Q12H); and therapy for cough relief and fever prevention consisted of Chinese herbal decoction.

● **RESULTS:** A 35-year-old male suddenly suffered pain, photophobia, and tears in his right eye for one day without systemic COVID-19 symptoms. Patient was diagnosed with keratitis, which was seemingly different from common keratitis. Ganciclovir eye drop was initiated. The corneal scraping test for COVID-19 was positive. The chest CT images were abnormal confirming the diagnosis of COVID-19 infection. The antiviral and antibacterial therapies were initiated. Chinese herbal therapy was used for cough relief and fever prevention. After roughly two weeks, patient recovered from COVID-19.

● **CONCLUSION:** A new type of keratitis, atypical keratitis, is a clinical manifestation of COVID-19, and this clinical manifestation could appear 3d earlier than fever and cough. The earlier a COVID-19 clinical manifestation is identified, the earlier can a patient be directed to stay at home, and significantly fewer people would be infected.

● **KEYWORDS:** keratitis; first clinical manifestation; COVID-19; atypical keratitis

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INTRODUCTION

Per the latest date from the World Health Organization, there were a total of 93 217 287 COVID-19 cases confirmed in more than 100 courtiers and 2 014 957 deaths globally (2.16% death rate), and this disease is rapidly spreading (https://www.who.int). This rapid spread is due to the virus's high contagion. The reproduction number (R0) of COVID-19 is roughly 3, indicating that this disease could spread exponentially[1-2]. The incubation period of COVID-19 is 2-14d[3], and the serial interval of COVID-19 is roughly 4.6d[4]. Reasonably assuming that COVID-19 transmissions among people only happen during the incubation period (because once a person has symptoms, he would be quarantined so that he could not transmit virus to others). During the incubation period, *e.g.*, 10d, 1 person infects 3 "R0" people. If COVID-19 symptoms are identified and patients are quarantined at home

one day earlier, the R0 would be reduced to 3×9/10=2.7. This 0.3 (3.0-2.7) difference in R0 makes exponentially difference in the numbers of infected people (infected people =$R0^{(n-1)}$, *n*: the generation of the infection; Table 1). If an infected patient is quarantined one day early, it will prevent roughly 1140 people from being infected in 32d, and roughly 1 190 000 people from being infected in 60d (Table 1). Therefore, even one day early to identify COVID-19 symptoms will significantly decrease the number of infected patients.

Almost all countries in the world do not mandate their residents to get COVID-19 test. COVID-19 symptoms are the only way to indicate that a person gets infected. Thus, how early a patient is quarantined depends on how early the symptoms appear. The early symptoms of COVID-19 include fever, cough, shortness of breath, persistent pain or pressure in the chest, confusion or inability to arouse, and bluish lips or face. However, this symptom list is not all-inclusive. It is critically important to identify any symptom of the infection as early as possible so that the infected people can 1) be directed to stay at home to stop the virus from exponentially spreading, and 2) get tested and treated immediately to reduce the lung damages. Considering no effective antivirals for the overwhelming infections, the most effective way of prevention is self-quarantine as soon as a COVID-19 symptom(s) is/are identified. Therefore, reporting a new symptom associated with COVID-19 infection is of both social and clinical significance. Here we report a case, in which keratitis is the first clinical manifestation of COVID-19 that occurred 3d earlier than the common COVID-19 symptoms.

Table 1 The number of patients infected with COVID-19 with different reproduction number

Generation	Days	The number of patients infected with COVID-19				
		R0=3.0	R0=2.7	R0=2.4	R0=2.1	R0=3.0/R0=2.1
1	0	1	1	1	1	1
2	4.6	3	3	2	2	1
3	9.2	9	7	6	4	2
4	13.8	27	20	14	9	3
5	18.4	81	53	33	19	4
6	23	243	143	80	41	6
7	27.6	729	387	191	86	8
8	32.2	2.19×10^3	1.05×10^3	459	180	12
9	36.8	6.56×10^3	2.82×10^3	1.10×10^3	378	17
10	41.4	19.7×10^3	7.63×10^3	2.64×10^3	794	25
11	46	5.90×10^4	2.06×10^4	6.34×10^3	1.67×10^3	35
12	50.6	17.7×10^4	5.56×10^4	1.52×10^4	3.50×10^3	51
13	55.2	5.31×10^5	1.50×10^5	3.65×10^4	7.36×10^3	72
14	59.8	1.59×10^6	4.05×10^5	8.77×10^4	1.55×10^4	103
15	64.4	4.78×10^6	1.09×10^6	2.10×10^5	3.24×10^4	147
16	69	1.43×10^7	2.95×10^6	5.05×10^5	6.81×10^4	211
17	73.6	4.30×10^7	7.98×10^6	1.21×10^6	1.43×10^5	301
18	78.2	1.29×10^8	2.15×10^7	2.91×10^6	3.00×10^5	430
19	82.8	3.87×10^8	5.81×10^7	6.98×10^6	6.31×10^5	614
20	87.4	1.16×10^9	1.57×10^8	1.68×10^7	1.33×10^6	877

The serial interval of COVID-19 is roughly 4.6d. The reproduction number (R0) of COVID-19 is roughly 3.0. If the patient is quarantined at home one day earlier, R0=2.7; 2d earlier, R0=2.4; 3d earlier, R0=2.1.

SUBJECTS AND METHODS

Ethical Approval This study was performed at the Department of Ophthalmology, the Hubei Provincial Hospital of Traditional Chinese Medicine and Department of Integrated Traditional Chinese and Western Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China. The study was approved by the hospital ethics committee. All participating individuals signed the informed consent.

Patient, Medical Examinations, and Therapies A 35-year-old male suddenly suffered pain, photophobia, and tearing in his right eye and was seen physicians at the Hubei Provincial Hospital of Traditional Chinese Medicine (Medical ID: 3897813) and the Union Hospital in Wuhan on January 8, 2020 (Medical ID: 3794961). Regular slit lamp examination, corneal scraping test, and chest computed tomography (CT) were performed. The ophthalmologic treatment included ganciclovir eye drop (50 mg/mL, 6 times/d)[5]. The treatment for diarrhea included Guifu Lizhong pills (Honey pills, a traditional medicine, 3 times a day for a total of 2d). The antiviral therapy consisted of oseltamivir 75 mg capsule Q12H[6]; therapy preventing bacterial infection consisted of azithromycin 250 mg tablet QD and moxifloxacin 0.4 g tablet Q12H; and therapy for cough relief and fever prevention consisted of Chinese herbal decoction (Maxing Shigan Tang from the *Treatise on Febrile Diseases*) 100 mL Q12H.

Statistical Analysis Microsoft Excel® 2010 was used for establishing the COVID-19 spread model and calculating the numbers of patients infected.

RESULTS

Day 1 A 35-year-old male ophthalmologist suddenly suffered pain, photophobia, and tears in his right eye for one day. No systemic COVID-19 symptoms.

Day 2 He was diagnosed with keratitis, which was seemingly different from common keratitis under a slit lamp microscope (Figure 1A). Specifically, it seemed like a viral keratitis, and the corneal inflammation looked distinct from common keratitis (Table 2). In the lower part of the right eye cornea, a shallow white turbid focus could be seen, which was similar to ground glass, with a clear boundary, and a large number of fine particles could be seen on the surface of the focus. Ganciclovir eye drop was initiated (6 times/d). The corneal scraping test for COVID-19 was positive (Table 3), and patient was quarantined at home. Patient started to feel fatigue.

Table 2 Three types of established viral keratitis

1	Herpes simplex viral keratitis	It is mostly accompanied by herpes in the eyelid area, and corneal fluorescence staining for the first time is mostly dendritic.
2	Herpes zoster viral keratitis	Accompanied by a blistering rash on one side of the face.
3	Adenoviral keratoconjunctivitis	Mostly binocular onset, and there is obvious conjunctivitis in combination. In the early stage, conjunctivitis was mainly present, and corneal lesions appeared in about 2wk.

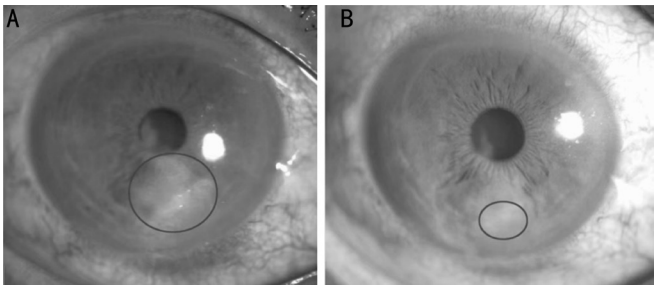

Figure 1 The images of the corneal lesion before and after the treatment A: In the lower part of the right eye cornea, a shallow white turbid focus can be seen, similar to ground glass, with a clear boundary; B: The size and color of the shallow white turbid focus became significantly smaller and lighter, respectively.

Table 3 Laboratory results (January 19, 2020)

Laboratory test	Result
White blood cell count, $\times10^9$/L	3.37↓
Red blood cell count, $\times10^9$/L	4.55
Neutrophil count, $\times10^9$/L	1.86
Lymphocyte count, $\times10^9$/L	1.15
Haemoglobin, g/L	144
Platelet count, g/L	162
Influenza A virus nucleic acid	Negative
Influenza B virus nucleic acid	Negative
NCovORFlab	Negative
Corneal scraping for COVID-19	Positive

Day 3 Slit lamp examination showed that the white turbidity in the lower part of corner of the right eye cornea became slightly paler, and the fine particles on the surface of the lesion were significantly reduced. The keratitis the symptoms were significantly relieved 24h later ganciclovir was initiated. Pain, photophobia and tearing were also significantly relieved. Patient continued feeling fatigue and started to suffer fever, cough, and discomforts.

Day 4 (From Afternoon) Slit lamp examination showed that the white turbidity in the lower part of corner of the right eye cornea became significantly smaller and paler, and the fine particles on the surface of the lesion disappeared (Figure 1B). The eye symptoms disappeared. Patient experienced fever, headaches, and fatigue. The body temperature was 37.5°C. After drinking a lot of boiled water and sweating, fever and headache were slightly relieved. By that time, it was officially reported that viral pneumonia of unknown etiology, whose symptoms includes fever and cough, might break out in Wuhan, Hubei Province, China. The patient received chest CT. The CT results showed no abnormalities (Figure 2A).

Day 5 No ophthalmology symptoms. Ganciclovir eye drop was discontinued. Fever, headaches, fatigue disappeared.

Day 7 No ophthalmology symptoms. Patient experienced nausea and diarrhea (water-like, 2 to 3 times/d). Patient took 50 pills of Guifu Lizhong pills three times a day for a total of 2d, during which the daily number of diarrhea gradually decreased, normal stool formed, and nausea disappeared during these 2d.

Day 11 No ophthalmology symptoms. Dry cough.

Day 12 No ophthalmology symptoms. The systemic symptom was significantly aggravated. The chest CT images (Figure 2B) were abnormal confirming the diagnosis of COVID-19 infection. Patient claimed that he had not gone to the Huanan Seafood Market. The antiviral therapy consisted of oseltamivir 75 mg capsule Q12H; therapy preventing bacterial infection consisted of azithromycin 250 mg tablet and moxifloxacin 0.4 g tablet Q12H; and therapy for cough relief and fever prevention consisted of Chinese herbal decoction (Maxing Shigan Tang from the *Treatise on Febrile Diseases*) 100 mL Q12H.

Day 14 No ophthalmology symptoms. CT showed no enlargement of the lung lesion (Figure 2C). Dry cough was alleviated. The therapies remained unchanged.

Day 19 No ophthalmology symptoms. Oseltamivir, azithromycin, and moxifloxacin were discontinued.

Day 20 No ophthalmology symptoms. Dry cough disappeared. The pharynx was still itchy, and the lung lesions were obviously reduced and faded (Figure 2D). Maxing Shigan Tang was discontinued (all the medications were discontinued).

DISCUSSION

It has been clear that transmissions of COVID-19 were through respiratory tract and digestive tract[7-8]. Recently, researchers modeled the spike protein and identified the receptor for COVID-19, and indicated that angiotensin-converting enzyme 2 (ACE2) could be the receptor for this virus[9]. It was found that the expression of ACE2 is positive in cornea and conjunctiva, and ACE2 can bind to the spike proteins of severe acute respiratory coronavirus virus 2 (SARS-CoV). In addition, previous studies detected the SARS coronavirus from tears[10]. However, there is no evidence indicating that the cornea and conjunctiva are one of the transmission routes of COVID-19. In this case report, we described a distinct keratitis that was the first clinical manifestation in COVID-19 infection. It was not

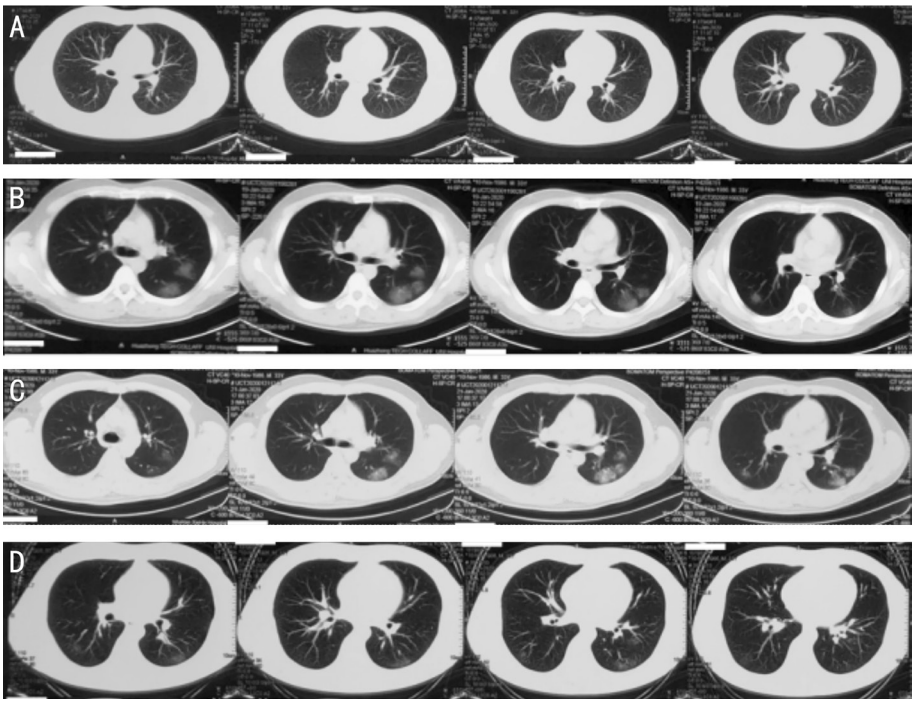

Figure 2 Chest computed tomography images A: Day 4, the finding of chest CT images was normal; B: Day 12, the typical finding of chest CT images was bilateral ground-glass opacity, especially on the left; C: Day 14, compared with the previous images, bilateral glass opacity did not increase; D: Day 20, bilateral ground-glass opacity had been resolved.

until 3d later that common symptoms of COVID-19 appeared. These pieces of evidence indicate that indeed the cornea and conjunctiva are one of the transmission routes of COVID-19, and support the use protective goggles.

There are 3 clinically established types of viral keratitis (Table 2). However, our case is distinct from these established types prompting us to perform a COVID-19 corneal scraping examination (Table 3). Our initial assessment on this case was that it was most likely and most reasonably a COVID-19 infection. The positive result from the corneal scraping examination confirmed our assessment. Our case was consistent with the report by Cheema *et al*[11], in which keratoconjunctivitis is the initial medical presentation of COVID-19. Further, Sansome and Lin[12] found that there has been a surge in eye care following the COVID-19 outbreak.

All coronaviruses are positive-sense single-strand RNA viruses that replicate their genomes using an RNA-dependent RNA polymerase (RdRp)[13-14]. The RdRp in coronaviruses is a well-established drug target; the active site of the RdRp is highly conserved among positive-sense RNA viruses[15]. These RdRps have low fidelity allowing them to be recognized by a variety of modified nucleotide analogues as substrates[16]. Thus, such nucleotide analogues were often used as anti-virals to inhibit RNApolymerase, which catalyzes RNA replication[17-20]. Recent study showed that the ganciclovir triphosphate from ganciclovir completely terminated the polymerase reaction in coronaviruses using the RdRp[21]. This potency in inhibiting coronaviruses replication, we believe, is the underneath mechanism that the symptoms in our case were relieved after using ganciclovir.

The limitation of our study is that we did not sequence the COVID genome, which otherwise would be among the few COVID-19 genomes sequenced at the beginning of the pandemic in Wuhan. Such sequence could provide clinical insight into the treatment[22], especially at that time, no lab protocols, no established therapies, and no clinical experiences could be followed. Nevertheless, we used our professional judgment to treat our patient based on several aspects. The results from corneal scraping examination confirmed our initial prediction, and the recent evidence on ganciclovir lends support to our use of ganciclovir in this case[21]. In conclusion, a new type of keratitis, atypical keratitis, is a clinical manifestation of COVID-19, and this clinical manifestation could appear 3d earlier than fever and cough. The earlier a COVID-19 symptom is identified, the earlier can a patient be directed to stay at home, and significantly fewer people would be infected.

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Conflicts of Interest: Zuo DM, None; **Xue LP,** None; **Fan H,** None; **Yang SL,** None; **Li LC,** None; **Luo JH,** None; **Zang S,** None; **Xiao J,** None.

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