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Immune characteristics of human immunodeficiency virus/severe acute respiratory syndrome coronavirus 2 coinfection: A case report and mini-review

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Abstract

Since its first appearance in Wuhan, China, severe acute respiratory syndrome coronavirus 2 has rapidly spread throughout the world and has become a global pandemic. It remains unclear whether people living with human immunodeficiency virus are at an increased risk of coronavirus disease 2019 and severe disease manifestation; until now, the evidence regarding the outcomes from severe acute respiratory syndrome coronavirus 2 infection in people living with human immunodeficiency virus is still limited and conflicting. The clinical characteristics of seven patients of family cluster-onset coronavirus disease 2019 were reported, including the immune characteristics of one patient of human immunodeficiency virus/severe acute respiratory syndrome coronavirus 2 coinfection. In the patients of human immunodeficiency virus/severe acute respiratory syndrome coronavirus 2 coinfection, about 2 weeks after infection, it was observed that CD4 and CD8 count showed a downward trend and that of CD8 is more obvious; at the same time, lymphocytes showed a slight increase. CD4, CD8, and lymphocytes are in the plateau period from the second week to the fourth week. About 4 weeks after infection, all showed an increase, in which anti-coronavirus combined with antiviral therapy were given. The time for Nucleic Acid Testing to present as negative was 51 days. The other six patients in the family were non–human immunodeficiency virus infected, the familial cluster received parallel treatment, and the median time for the Nucleic Acid Testing to present as negative was 29 days. The patient of human immunodeficiency virus/severe acute respiratory syndrome coronavirus 2 coinfection presents an immune state of CD4's and CD8's dual lymphatic depletion. Human immunodeficiency virus should still be regarded as an important factor in future risk stratification models for coronavirus disease 2019.

Keywords

Coronavirus disease 2019, human immunodeficiency virus infection, CD4T lymphocytes, immunodeficiency

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Introduction

As of December 2019, an outbreak of pneumonia of unknown origin was first reported in Wuhan, China.[1,2] The cause had been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly identified coronavirus, which was officially named as COVID-19 (coronavirus disease 2019) by World Health Organization (WHO).[3] Following 17 February, about 109,922,763 cases have been confirmed, and reports have corroborated over 2,422,254 cases of deaths. Several medical comorbidities have been identified as risk factors for COVID-19, such as diabetes, hypertension, and cardiovascular disease (CVD). Earlier reports proposed that human immunodeficiency virus (HIV)–related immunosuppression could paradoxically

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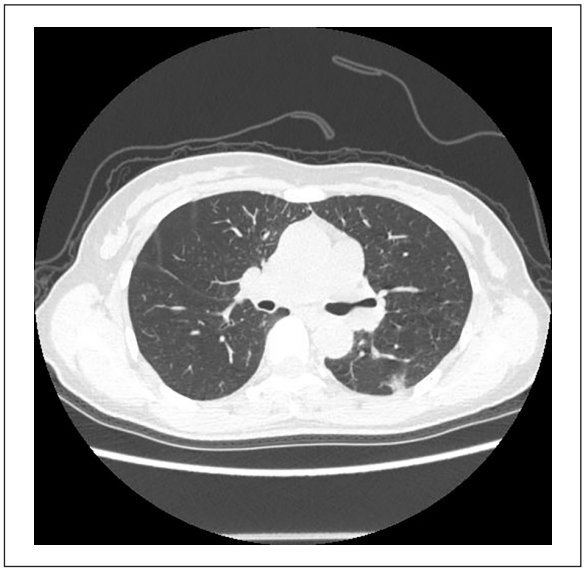

Image 1. Multiple GGO under the left pleura of the lower left lung.

protect against severe manifestation of COVID-19.[4–7] This research investigates the clinical and immune features of the new HIV diagnoses in patients with COVID-19, including a mini-review of related literature. These findings will facilitate understanding of the immunology and its implications for therapy of HIV/SARS-CoV-2 coinfection.

Case

As a suspected case of COVID-19, a 51-year-old female patient was admitted at the hospital on 30 January 2020, presented with the symptoms of a "cough, runny nose, and a fever for 2 days" and a maximum body temperature of 37.8°C. The family cluster included seven family members: the patient's husband, daughter, son-in-law, son, two grandchildren. Within this group, the oldest was 65 years old and the youngest was 2 years old. The history reported close contact between the members within the past 10 days. Their upper respiratory tract viral RNA tests were positive for SARS-CoV-2 RNA.

SARS-CoV-2 RNA detection method: Duplex Real-Time PCR Diagnostic Kit for Rapid Detection of 2019-nCoV ORF1ab/Ngene.

Examination of the patient of HIV/SARS-CoV-2 coinfection on the day of admission: T 37.2°C, P 86 times/min, R 20 times/min, BP 118/81 mm Hg, the results on 30 January showed. Conscious, no skin rashes or subcutaneous bleeding points on the whole body, superficial lymph nodes in the whole body did not display swelling upon clinical touch examination, the breath sounds of both lungs were thick, and no moist rales or rhonchi were heard in the lungs. An abdominal examination revealed no abnormalities. Blood routine test: White blood cells 4.02 10×9/L, lymphocyte count 1.03 10×9/L, c-reactive protein (CRP) 0.3 mg/L, Calcitonin <0.05 ng/mL, and erythrocyte sedimentation rate 14 mm/h. The arterial blood gas analysis was normal. A chest computed tomography (CT; Image 1) showed multiple ground glass nodule (GGN) under the left lower lobe pleura. HIV antibodies tested positive. The result on 31 January is displayed as the Western blotting (WB) band gp160 gp120 p66 p55/51gp41p31p24p17, which indicated that the HIV-1 antibody was positive and HIV-RNA 27,544 cp/mL. CD4 421 cells/μL, CD8 626 cells/μL, $CD4^+$/CD8 0.67 (reference: CD4 404-1612 cells/μL, CD8 220-1129 cells/μL). The result on 5 February is that HIV-1 resistance measurement shows sensitivity to tenofovir (TDF), lamivudine (3TC), lopinavir/ritonavir (LPV/r), and 16 other drugs. Interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor–alpha (TNF-α) were not tested. The patient, who had no history of people living with human immunodeficiency virus (PLWH), had been separated from her husband for an approximate 2 years and confirmed HIV transmission from her male partner. The six family members were tested for HIV antibodies, her husband received testing twice, and all presented negative results.

HIV antibodies detection method: the Abbott chemiluminescence method, ZhongxiaoKeju colloidal gold method, Meieril colloidal selenium method, and so on. Serum Ab-IgM, Ab-IgG detection method: colloidal gold method.

On 22 January 2020, the patient's daughter came into proximity with her, arriving from a residence in Hubei, China, after a family gathering, and her daughter developed fever the day after. A cluster of infections was reported in Hubei, while other family members had no history of stay in other places.

All patients received electrocardiogram (ECG) examination before receiving drug treatment; particular attention was given to the ECG monitoring of the patient receiving hydroxychloroquine sulfate.

The patients used in this research project were obtained from Longtan Hospital of Guangxi Zhuang Autonomous Region (LT Hospital): LT Hospital is supported by the Infectious Disease Medical Quality Control Center, Guangxi, China, which is based at Guangxi Zhuang Autonomous Region Health Committee of China. The study protocol was reviewed and approved by the Ethics Committee of LT Hospital (No. 20201002). All participants, or legal guardians of participants if necessary, provided written informed consent.

According to the Treatment Program issued by the National Health and Health Commission of China,8 the patients in this cluster clearly have only one inducing case; no other potential sources of infection are plausible. This conclusion is based on the history of the first case imported from the Wuhan epidemic area in Hubei, China, one day before the onset of illness. Along with a close contact history, it is clear that the patient of HIV/SARS-CoV-2 coinfection and six family members had fever, imaging evidence

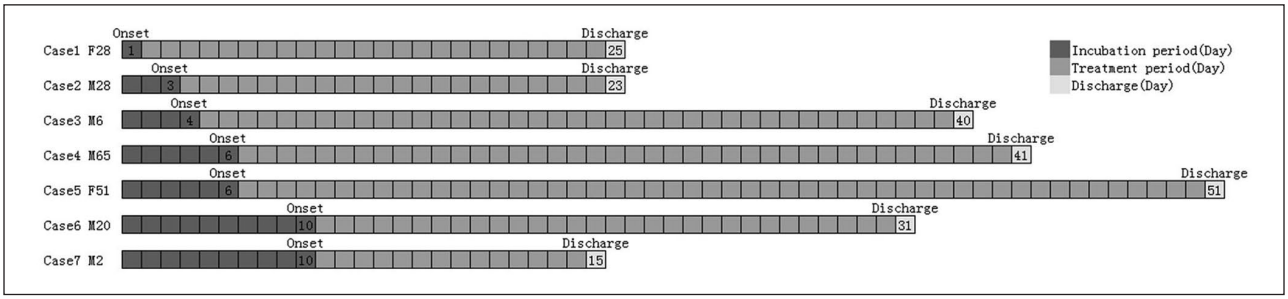

Figure 1. Detailed information on exposures and dates of illness onset in cluster, including seven cases.
[a]Index case onset time: January 23, 2020.

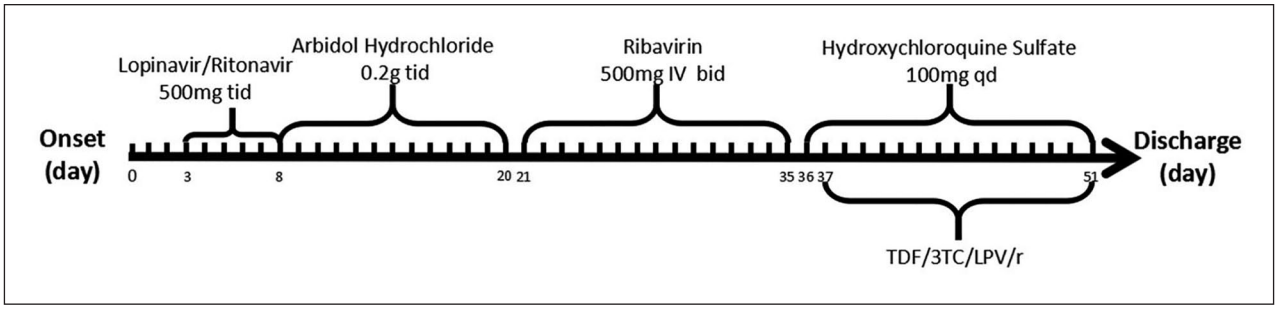

Figure 2. Detailed treatment of this case.
Above the time axis is the medication and time, dosage, and usage of sympathetic treatment for this case, and below the time axis is the medication and time of ART.
[a]According to the Treatment Program issued by the National Health and Health Commission of China.

of pneumonia, low or normal white blood cell count or low lymphocyte count, arterial blood gas analysis that was normal, and SARS-CoV-2 RNA positive detection by upper respiratory tract samples. In light of the above diagnostic criteria, the case was diagnosed as COVID-19 common type and an asymptomatic period of HIV infection; her husband was diagnosed with COVID-19 common type, type 2 diabetes; the other five cases were diagnosed as COVID-19 common type (Figure 1). Accordance with the Treatment Program of China,[8] compassionate drug use was given to seven family members based on in vitro evidence of SARS-CoV-2 inhibition. Figure 2 shows the detailed treatment of this case during hospitalization. When SARS-CoV-2 RNA test continues to be positive for more than 7 days or when adverse reactions occur, the antiviral drugs (lopinavir/ritonavir, arbidol, ribavirin, hydroxychloroquine) will be changed or continued after consultation by the expert group members. Figure 3 lists the CRP test results of this case during hospitalization. Figure 4 lists the results of the SARS-CoV-2 RNA test, which continued to be positive, and serum Ab-IgM, Ab-IgG test which continued to be negative. Figure 5 lists the comparison reports of CD4, CD8, and lymphocytes during the treatment. The chest CT lesions increased slightly 5 days after admission (Image 2), a small amount was gradually absorbed 16 days after admission, and the chest CT lesions still existed 35 days after admission (Image 3). A combined highly effective antiretroviral therapy (ART) on the 37th day after onset, the following drugs were administered: TDF 300 mg once/day, 3TC 300 mg once/day, LPV/r 200/50 mg twice/day, and so on. Fourteen days after starting ART, HIV-RNA decreased to 1723 cp/mL, CD4 rose to 454/μL. On the 50th and 51st days after onset, SARS-CoV-2 RNA test was negative, twice in succession, and chest CT lesions were completely absorbed at 51 days after admission (Image 4).

In this case, a follow-up review for COVID-19 was conducted on the second and fourth weeks after discharge. Chest CT (Image 5) showed no abnormalities, and SARS-CoV-2 RNA, Ab-IgM, and Ab-IgG testing were negative, and COVID-19 has been cured. After continued 12 months of ART (TDF, 3TC, and LPV/r), the HIV-RNA decreased to 0 cp/mL, CD4 increased to 539 cells/μL, and CD8 increased to 424 cells/μL in the follow-up review on 7 December 2020.

Discussion

In this case, the clustered incidence of COVID-19 among this family is clear. It can be inferred that the infected virus strains are the same, and the seven patients received parallel treatment in the same hospital. With an approximate gestation period of 6 days, this case is typical, originating during close contact with the source case progressing to the onset of symptoms. This is similar to the communication dynamics reported from Wuhan, China,[9] and the onset time was 5.2

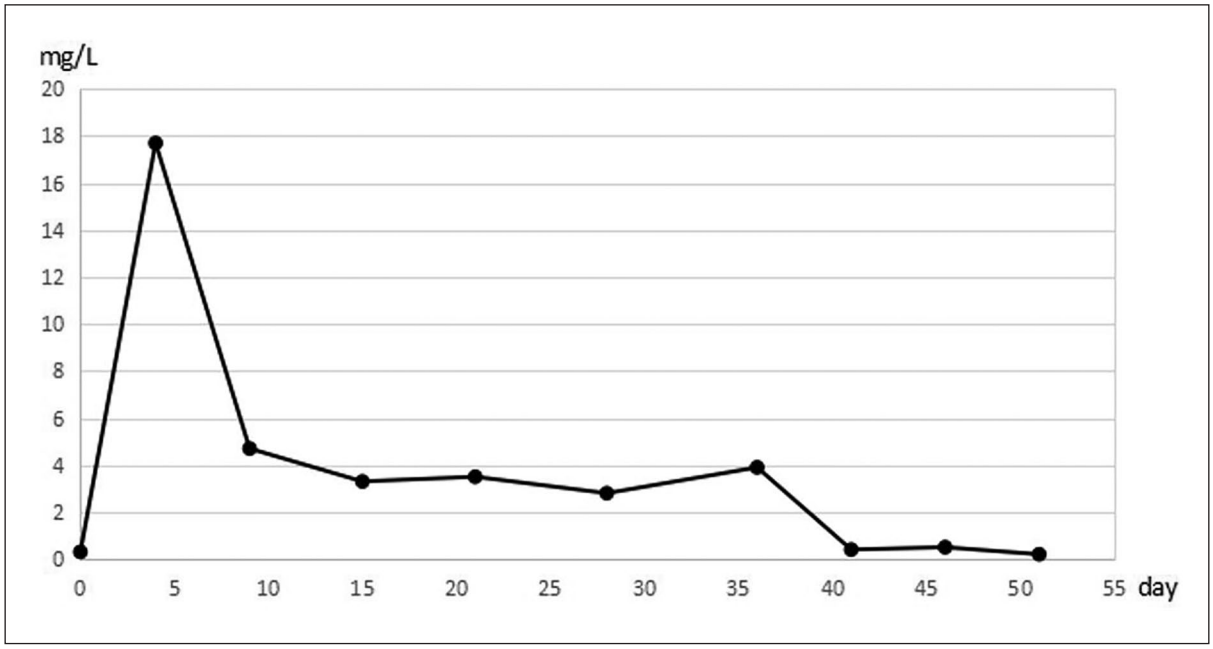

Figure 3. Monitoring of CRP in this case.
30 January 2020: 0.3 mg/L (The initial), 3 February 2020: CRP 17.7 mg/L (The highest), and 21 March 2020: CRP 0.2 mg/L (The lowest).

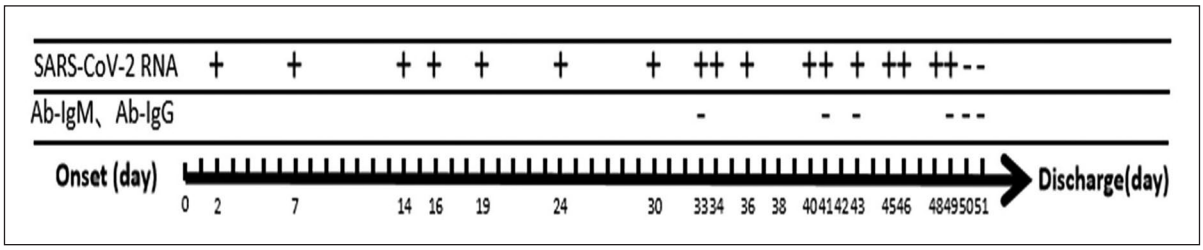

Figure 4. Detection of SARS-CoV-2 RNA, Ab-IgM, and Ab-IgG in this case.

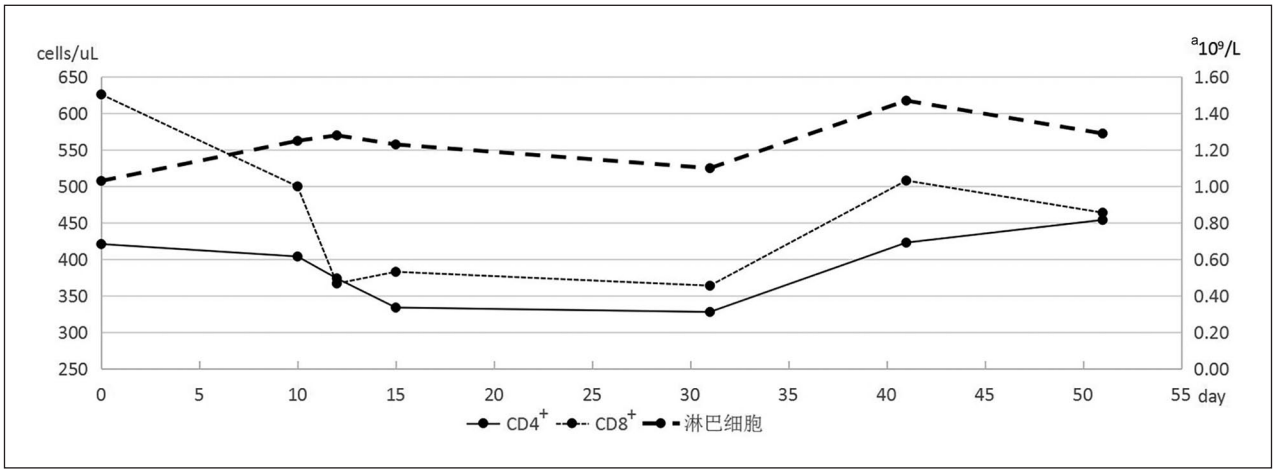

Figure 5. Monitoring of T lymphocytes in this case.
[a]30 January 2020: lymphocyte count 1.03 10 × 9/L, 31 January 2020: CD4+ 421 cells/μL, and CD8+ 626 cells/μL, CD4+/CD8+ 0.67 (Reference CD4+ 404–1612 cells/μL, CD8+ 220–1129 cells/μL).

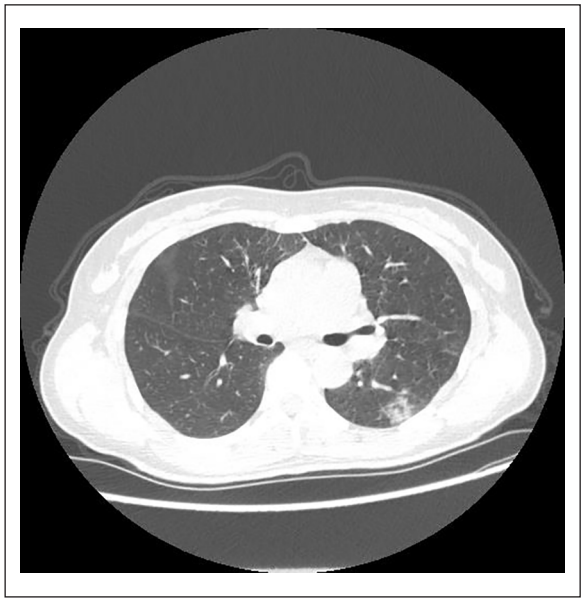

Image 2. GGO shadow increases and the range increases.

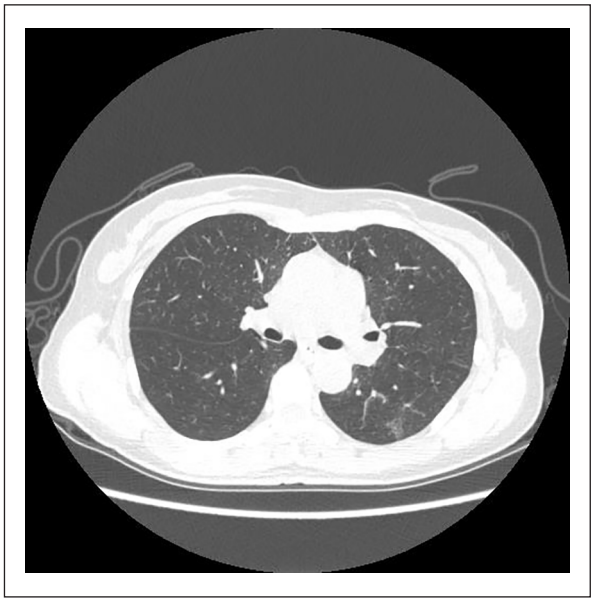

Image 3. Lesion still exists.

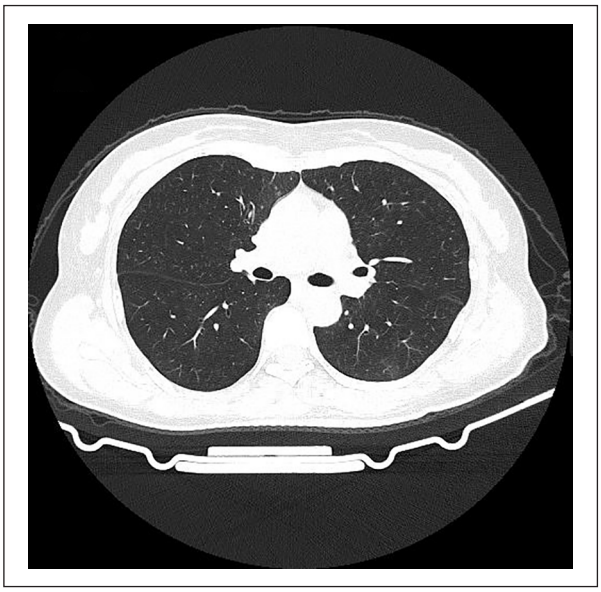

Image 4. Lesion was absorbed.

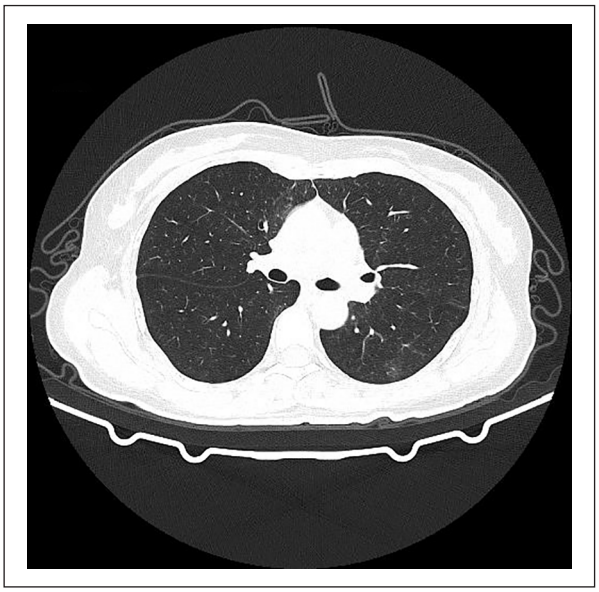

Image 5. Fourth week after discharge showed no abnormalities.

(95% confidence interval (CI): 4.3–7.5) days; the time from onset to negative Nucleic Acid Testing (NAT) was 51 days for the HIV/SARS-CoV-2 coinfection patient, which was significantly longer than the rest of the six members in the family cluster who received negative NAT after a median time of 29 days. One report from Wuhan, China,[10] declared an average time from onset to negative NAT in the infected population was 24.7 days (95% CI: 22.9–28.1), with a coefficient of variation of 0.35. In another report from Wuhan, China,[11] the time from onset to negative NAT was 20.0 days (interquartile range (IQR): 17.0–24.0). From this, it can be understood that the median positive to negative time for NAT of other members of the family is similar to that in domestic reports. Under the consistent conditions of strain virulence, latent infection to onset time, and treatment compared with other family members, it is speculated that HIV/SARS-CoV-2 coinfection is the main relevant factor for the patient's prolonged virus clearance.

As far as we know, CD4 and CD8 show a protracted and tortuous decline after HIV infection. The rate of decline from

CD4 is relatively large, gradually increasing in distance from CD8, which eventually leads to the inversion of the ratio of CD4/CD8; therefore, early HIV infection mainly causes damage of CD4. According to Xiaorong Peng,12 when COVID-19 and HIV collide on the immune system, they share CD4 losses. For the HIV/SARS-CoV-2 coinfection patient, in line with our clinical observations, early anti-coronavirus treatment was given with general or specific compassionate drug use, from day 1 to day 12; CD8 decreased rapidly, from the second week to the fourth week of onset; and CD4 and CD8 reached a plateau period. We also observed the changes in lymphocytes; interestingly, the lymphocytes did not show a gradual decline, in the early HIV infection, but a slight increase; a plateau period is also formed from the second week to the fourth week. Our description supports that the early new strain of coronavirus mainly attacks CD8, and they decrease rapidly, but the patient's lymphocytes have not decreased simultaneously. The latest autopsy results show that[13] an important feature of COVID-19 is lymphocyte depletion, and lymphocytes (especially CD8 T lymphocytes) decrease or absence and phagocytosis can be seen in all hematopoietic organs of the deceased. The autopsy system reports showed that the lymphocyte count was negatively correlated with CD4 and CD8. A meta-analysis showed[14] that 378 HIV/SARS-CoV-2 coinfection cases have so far been reported globally, 244 had complete personal information, 228 out of 244 were on ART before being diagnosed with COVID-19. The new HIV diagnosis in patients with COVID-19 helped to link CD4 and CD8 to each other. No report was seen in the previous series. Our report describes a case of double lymphatic depletion for the first time.

In the non-PLWH population, two studies reported that patients with frequent severe disease had increased IgG response and higher plasma levels of total antibodies, which was associated with a worse outcome.[15,16] The meta-analysis[17] suggests that serum CRP provides good discrimination between severe COVID-19 and non-severe COVID-19 infections with an optimal cutoff of 33.55 mg/L, yielding a sensitivity of 89.5% and a specificity of 89.5%. The new HIV diagnosis in patient with COVID-19 is without antiviral therapy, the baseline of cellular immunity is CD4 421/mL and CD4/CD8 0.67, and insufficient cytokine production may be confirmed by low levels of CRP (0.2–17.7 mg/L) throughout the onset. The mildly reduced cellular immunity resulted in adaptive immunity, which may impede the generation of cytokine storms. However, excessive suppression of cellular immunity may also reduce the immune system's ability to eliminate viruses, resulting in a continual positive for SARS-CoV-2 RNA testing. In this case, ART was chosen to be given on the 37th day after onset, based on a chest CT imaging suggesting that lung lesions had been gradually absorbed and CD4 decreased to 328/μL. This case, which is combined with an HIV infection, is the most important reason for our meticulous selection of ART. Based on the following considerations, at present, there are no relevant guidelines or clinical experience to recommend a systematic timing and program for AIDS combined with COVID-19 in accordance to the ideal methodology for initiating ART. In the early stage of the patient, that is, when the immune baseline was close to normal, and regardless of ART's potential to rebuild or improve immune function, it is unclear whether immune reconstitution inflammatory syndrome (IRIS) and the cytokine storm of COVID-19 in HIV-infected people may be hampered because of the lack of immune inflammatory factors.

This patient presented a double lymphatic depletion, and HIV/SARS-CoV-2 coinfection will make immune changes more complicated. Clinical evidence has shown that disease severity and mortality are associated with older age and underlying comorbidities, such as diabetes, hypertension, and CVD. Earlier reports proposed that HIV-related immunosuppression could paradoxically protect against severe manifestation of COVID-19. The mate analysis[14] showed that CD4 count <200 cells/μL increases the risk of progression to severe COVID-19 by almost 5. HIV-related immunosuppression may increase the risk of severity of COVID-19 instead confer protection. As severe outcomes in HIV/SARS-CoV-2 coinfection, two patients of HIV/SARS-CoV-2 coinfection were reported[18] in China, CD4 count <50 cells/μL, and the critical cases of COVID-19 were cured. Suwanwongse and Shabarek[19] suggested that CD4 count, HIV viral load, and ART regimen may not impact COVID-19 outcomes. The meta-analysis[20] of 38 studies showed that HIV may not associated with the composite poor outcome which is comprised of severe COVID-19, intensive care unit (ICU) admission, the need of mechanical ventilation, and mortality. This association was influenced by hypertension and diabetes. Currently, the evidence regarding the link between HIV and COVID-19 is still limited and conflicting.[21]

Conclusion

In this case, use of multiple compassionate drugs for 51 days and COVID-19 NAT continued as negative. It is suggested that the removal of SARS-CoV-2 in this case is still based on the body's immune clearance. The investigation of the immune mechanism of COVID-19 combined with HIV infection and the timing and optimum schedule of initiation of ART will require further study with a larger sample size.

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Author contributions

Aimei Liu, Jie Wei, and Yuanlong Xu conceived the study. Aimei Liu designed the study. Jie Wei collected clinical data. Guowei Wu

collected the X-ray images. Aimei Liu analyzed and interpreted the data. Dayong Huang, Kangyan Lv, Zhihao Meng, and Aimei Liu formulated the treatment regimen and analyzed the X-ray images. Junli Huang made the tables and figures. Liling Huang searched the literature. Jie Wei wrote the manuscript. Aimei Liu critically revised the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

Ethical approval to report this case was obtained from the Ethics Committee of Longtan Hospital of Guangxi Zhuang Autonomous Region, China (20201002).

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Consent for publication

All authors agreed to publish.

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Supplementary Materials

The source of the data in this paper is from Longtan Hospital, Guangxi Zhuang Autonomous Region; data are from hospital information system (HIS); and computed tomography (CT) images are from picture archiving and communication systems (PACS) system.

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