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CASE REPORT

COVID-19 induced immunosuppression leading to secondary infection in a non-HIV patient

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ABSTRACT

Lymphopenia and immune dysfunction in COVID-19 is increasingly recognized and studied. This case report details a secondary infection following lymphopenia with CD4+ count drop in a COVID-19 patient with no history of immunosuppression or infection with HIV. The mechanism of lymphopenia, both CD4+ and CD8+ T cell count drops, in COVID-19 needs further study.

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KEY WORDS: COVID-19; Immunosuppression; Lymphopenia; Coinfection; HIV.

The literature has shown that COVID-19 patients commonly have lymphopenia, a decrease in CD4+ and/or CD8+ T cells, that may increase susceptibility to secondary bacterial infection. Here, we report a secondary pneumonia in a non-HIV COVID-19 patient with new CD4+ T cell depletion.

Case report

On March 19, 2020, a 54-year-old female nurse, with a past medical history of obesity and hypertension screened positive for COVID-19 with real time polymerase chain reaction (RT-PCR) oropharyngeal testing and was admitted to the National Hospital for Tropical Diseases in Hanoi, Vietnam solely with fatigue. Upon examination, she had normal vitals with a normal physical exam. Testing included HIV viral quantitation RT-PCR, and chest X-ray, which were also negative. Following national guidelines for COVID-19, lopinavir-ritonavir (400 mg and 100 mg, respectively) was given twice a day for the first day. On the second day, IV ceftazidime (4 g/day) hydroxychloroquine (200 mg × 3 pills/day) and azithromycin (500 mg × 1 pill/day).

On day three of hospitalization, the patient reported new-onset diarrhea that occurred (6-7

times/day). As a result, lopinavir-ritonavir was discontinued with suspicion for medication side effect. Although her vitals and laboratory testing were normal, the second COVID-19 RT-PCR given showed positivity with the chest CT showing lesions indicative of viral pneumonia.

On day five of hospitalization, the patient had sudden onset of productive cough. The patient's diarrhea improved to 3-4 times/day, although she was still fatigued. Her body temperature increased to 38.0ºC; otherwise, her physical exam and other vitals remained unremarkable. However, the COVID RT-PCR came back negative. Her treatment regimen remained unchanged.

On day seven, despite a negative RT-PCR, the patient had a sudden onset of dyspnea, and was placed on nasal cannula (2 L/min). She reported exacerbated cough, increased fatigue, worsening of diarrhea (from 3-4 times per day to 5 times a day), pleuritic chest pain, and insomnia. Her laboratory tests disclosed a high level of fibrinogen (6.4 g/L) and D-dimer (978 ng/mL) consistent with a severe COVID infection. She also had a fever of 38.5 C. Due to worsening of symptoms, IV ceftazidime was discontinued, and IVIG (50 mL × 5/day x 3 days), imipenem/cilastatine (2 g/day × 5 days), and levofloxacin (500 mg/day × 5/day) were started. A CD4 count showed a low level of 319 ($\times 10^9$ cells/L). Repeated CT chest showed revealed multiple consolidations and bilateral ground-glass opacities. Using the Matrix-Assisted Laser Desorption/Ionization-Time of Flight mass spectrometry identification method (MALDI-TOF) *R. mucilaginosa* (3+ or 100,000 CFU) was detected on Day 8 on blood agar medium. The antibiogram of *R. mucilaginosa* showed resistance only to clindamycin, rifampin, and azithromycin. The blood cultures also came back negative.

On day 10, although the patient was still required supplemental oxygen with nasal cannula (2 L/min), she no longer reported having dyspnea. Her cough frequency and sputum production decreased. Patient's diarrhea and fatigue reduced in intensity. The sputum culture, blood culture, and RT-PCR eventually returned negative. However, both D-dimer and fibrinogen were elevated at 1167 ng/mL and 6.28 g/L, respectively. Methylprednisolone was given from day 9 to day 13 of hospitalization. By day 21, her CD4 count went back to normal 615 ($\times 10^9$ cells/L), and all her vitals, signs and symptoms returned to normal, patient was discharged with outpatient follow-up with PMD.

Discussion

It is documented that patients with moderate to severe COVID-19 infection may have drastically reduced numbers of CD4+, CD8+, B cells, and NK T cells, secondary to maladaptive immune activation.[1] On Day 7 of our patient's hospitalization, the CD4+ count was 319 ($\times 10^9$ cells/L) but returned to normal with 615 ($\times 10^9$ cells/L) on Day 21 (Supplementary Digital Material 1: Supplementary Table I). She also had a significant decrease in lymphocytes between Day 5 and 7, from 1.74 to 0.91 ($\times 10^9$ cells/L). With no history of immunosuppression and a negative HIV test during her stay, this suggests that this is an immunological phenomenon to COVID-19 that predisposed her to a bacterial co-infection or superinfection in the hospital.

The species of bacteria identified using sputum cultures grown on blood agar was *R. mucilaginosa,* which was in a 3+ quantity. What we detected could be contamination, as *R. mucilaginosa* is a normal oral flora and the patient was put on antibiotics before the sample was obtained. Additionally, cultures for *R. mucilaginosa* were negative in the blood, and subsequent cultures thereafter was negative. However, patient's symptoms and laboratory results do indicate a bacterial pneumonia, which was successfully treated with IVIG, imipenem/cilastatin, and levofloxacin after switching from IV ceftazidime and azithromycin.

Conclusions

As of now, the mechanism of lymphopenia, both CD4+ and CD8+ T cell count drops, in COVID-19 needs further study. Firstly, lymphopenia may be caused by increased cell death. An interesting study performed a transcriptomic RNA-sequencing analysis in COVID-19 patients with lymphopenia and found that apoptosis and p53 cell death pathways were activated in lymphocytes of COVID-19 patients when compared to healthy individuals.[2] Secondly, cytokines or hy-

percytokinemia may play a role in lymphopenia in COVID-19. Proinflammatory cytokines such as TNF-alpha have been shown to cause lymphopenia by suppressing hematopoiesis.[3] Also, SARS-CoV-2 virus may be capable of entering T lymphocytes by binding to a T cell surface protein such as CD147 and may cause a direct cytopathic effect to lymphocytes.[4] Other possible mechanisms of lymphopenia in COVID-19 that need further study include lymphocyte exhaustion, possible bone marrow suppression by cytokines, or sequestration of lymphocytes in the lung with extensive infection.[3, 4]

References

1. Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, *et al.* Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. Immunology 2020;160:261–8.

2. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, *et al.* Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect 2020;9:761–70.

3. Fathi N, Rezaei N. Lymphopenia in COVID-19: therapeutic opportunities. Cell Biol Int 2020;44:1792–7.

4. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, *et al.* Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020;75:1564–81.

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