Perpetually Positive: Post-COVID Interstitial Lung Disease in an Immunocompromised Patient With Diffuse Large B-cell Lymphoma

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Abstract
As more patients recover from COVID-19 infection, long-term complications are beginning to arise. Our case report will explore a debilitating long-term complication, Post-COVID Interstitial Lung Disease (PC-ILD). We will introduce a patient who developed PC-ILD in the setting of diffuse large B-cell lymphoma, outlining a difficult hospital course, including a positive COVID-19 polymerase chain reaction (PCR) for more than 3 months. We will then discuss the human body’s physiological response to the virus and how our patient was not able to adequately mount an immune response. Finally, the pathophysiology of PC-ILD will be explored and correlated with the patient’s subsequent computed tomographic images obtained over a 3-month period. The difficult hospital course and complex medical decision-making outlined in this case report serve as a reminder for health care providers to maintain vigilance in protecting our most vulnerable patient population from such a devastating disease process.

Keywords
immunology, infectious disease, hematology, oncology, radiology/imaging, geriatrics

Introduction
In the United States, more than 33 million people have been diagnosed with COVID-19. While the majority of such patients only develop mild symptoms, such as loss of taste or smell, a small percentage of patients require hospitalizations, with some resulting in death. As of June 2021, more than 613,000 deaths (2%) due to COVID-19 have been reported.1 For those who recovered, the long-term sequela of complications are relatively unknown, yet are starting to arise.2,3 Our case report discusses one of the debilitating long-term complications, Post-COVID Interstitial Lung Disease (PC-ILD), in the setting of diffuse large B-cell lymphoma (DLBCL). The patient was treated with a regimen of rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) therapy for his DLBCL. Although he was in remission, the patient was leukodepleted, which inhibited his body’s ability to respond to an infection. Unfortunately, the patient contracted COVID-19, which persisted for >3 months with persistent positive COVID-PCR results. The patient then developed pulmonary fibrosis, which left him debilitated, with persistent desaturations requiring a high oxygen supplementation, consequently requiring hospice care. Our case highlights the importance of maintaining vigilance toward our most vulnerable patient populations.

Case
Our patient is a 69-year-old man with stage IV DLBCL who presented for syncope and worsening weakness. On admission, the patient tested positive for COVID-19 (PCR), and a few days later he experienced worsening respiratory distress. Throughout his admission, the patient remained febrile and required an increasing oxygen supplementation. Subsequent COVID-PCR lab results over the next 3 months persistently tested positive. Repeat computed tomographic (CT) scans showed worsening bilateral opacities (Figures 1-3). The Infectious Disease service believed that the patient had chronic inflammation from prior COVID-19 infection. The patient’s COVID-19 PCR cycle threshold was elevated at 35, indicating a low viral load. Given that the initial...
COVID-PCR positive result was 3 months prior, the Infectious Disease team did not believe that the patient was having an active COVID-19 infection and that the patient was not contagious. A thorough infectious workup was non-remarkable. Fungal studies, such as cultures, beta-d-glucan, and histoplasma, did not yield any significant results. A bacterial workup was also negative, which included repeated blood and sputum cultures for Legionella, Bordetella, Chlamydia, Mycobacterium, and Mycoplasma. Other viruses were also ruled out, including adenovirus, influenza, parainfluenza, metapneumovirus, and even coronavirus strains that are not COVID-19. The patient’s clinical status continued to deteriorate, desaturating to 83% on 5 L of nasal cannula. The patient eventually required 15 L of high-flow. The intensive care unit was consulted, and they recommended a steroid taper starting with prednisone 40 mg for 1 week, subsequently decreasing by 5 mg every 7 days. The patient’s oxygen requirement decreased to 5 L of nasal cannula. A repeat CT thorax demonstrated extensive pulmonary edema, as well as early pulmonary fibrosis (Figure 2). At the time, no established guidelines existed for the treatment of PC-ILD. We then decided to treat for PC-ILD with a higher dose of oral steroids. The patient received methylprednisolone 70 mg twice a day for 3 days. The patient’s respiratory status improved and he required less oxygen, eventually de-escalating to 4 L of nasal cannula. A CT thorax was repeated and showed an interval improvement in pulmonary edema, revealing a more extensive pulmonary fibrosis (Figure 3). A discussion regarding goals of care was conducted, and the patient was discharged to home hospice.

**Discussion**

A key feature in the physiological response to viruses is the production of memory B cells within the adaptive immune response. B cells are responsible for the generation of antibodies, which recognize the viral antigens during reinfection. B cells begin their development in the bone marrow, where certain signaling mechanisms stimulate hematopoietic stem cells to differentiate into B cells. Once mature, the B cells activate in secondary lymphoid organs, such as the lymph nodes, where it can undergo a T-cell-dependent activation. This process leads to the development of mature B cells and plasma cells that secrete antibodies. Another process would be T-cell-independent activation, where the B cells are activated with certain cell components like
bacterial polysaccharide. For the purpose of the discussion regarding COVID-19, we will focus on the T-cell-dependent B-cell activation.

Our patient was first diagnosed with DLBCL in June 2020. He then received 2 rounds of R-CHOP and selinexor chemotherapy in July, which left him in an immunocompromised state. During that time, his leukocyte count was 100 cells/mm³ with an undetectable absolute lymphocyte count (ALC). He then contracted COVID-19 in August, with a positive COVID-PCR recorded on August 2020. During the time that he contracted COVID-19, he demonstrated a slight improvement in leukocyte count of 7400 cells/mm³; however, his ALC remained low at 200 cells/mm³. Due to profound leukopenia, the patient’s disease course would be classified under a humoral response deficiency phenotype. Most immunocompromised patients belong to this phenotype, which is characterized by a deficient humoral response. Our patient was not able to mount a solid response against the virus. The course of his COVID-19 infection consisted mostly of shortness of breath and low-grade fevers. However, his shortness of breath had persisted for >3 months, progressively requiring increased oxygen supplementation. During his hospital course in September and October, he received 2 more cycles of R-CHOP and selinexor chemotherapy. Throughout this time, he had a leukocyte count of 100 cells/mm³ with an ALC of 100 cells/mm³. He initially required 2 L of nasal cannula, eventually escalating to 15 L of high-flow nasal cannula. He was then preemptively treated with high-dose methylprednisolone 70 mg, twice a day, for 3 days. Due to the relatively recent emergence of COVID-19, this treatment regimen was not available in literature at the time. Although leukopenic with an ALC of 100 cells/mm³, the patient may have still mounted an inflammatory response, thus responding very well with methylprednisolone, which greatly reduced his pulmonary infiltrates and oxygen requirement (Figures 2 and 3).

PC-ILD is a disease process that is slowly starting to emerge as COVID-19 survivors, particularly with difficult hospital courses, are starting to develop symptoms of persistent shortness of breath and hypoxemia, despite adequate treatment. The fibrotic changes, as seen in chest imaging, are similar to other fibrotic changes in the lung. The pathogenesis of PC-ILD revolves around the excessive and dysregulated release of matrix metalloproteinases during the inflammatory state, which leads to the degradation of structural proteins around the epithelial and endothelial linings of the lung. There is also an increase in fibroproliferation, leading to the deposition of excess collagen tissues within the lung parenchyma.

A hallmark finding in our patient is the development of pulmonary fibrosis, as demonstrated in subsequent CT thorax imaging obtained over the span of 4 months. The first imaging study (Figure 1) obtained on July 1 to evaluate lymphoma progression showed bilateral pleural infiltrates; however, there was no evidence of pulmonary fibrosis. A repeat CT thorax obtained on November, 2 months after initially testing positive for COVID-19, showed pulmonary edema and bilateral pleural infiltrates, as well as the early development of pulmonary fibrosis, mostly located in the posterior basal portion of the lung (Figure 2). A third CT thorax was obtained 3 weeks later, which showed a reduction in pulmonary edema and pleural infiltrates, revealing a more extensive pulmonary fibrosis (Figure 3). During the time the third CT thorax had been obtained, the patient finished a 3-day course of methylprednisolone, and he did not receive any diuretics. The patient demonstrated a great response to this empiric treatment of high-dose steroids, and his respiratory status clinically improved. However, the patient remained debilitated from the ongoing malignancy and difficult hospital course, eventually pursuing hospice. After an arduous 3 months of hospitalization, the patient was discharged to home hospice. The patient’s difficult hospital course serves as a reminder for health care providers to remain vigilant in protecting the most vulnerable patient population from debilitating infections, such as COVID-19.

**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.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

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

**Data Availability**

The data used upon this article are available upon request to the author for ethical and privacy reasons.

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