CLINICAL VIGNETTE

Pulmonary Masses Secondary to Cryptococcal Pneumonia in an Immunocompetent Patient after COVID-19 Infection: A Case Report

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Case

A 29-year-old healthy male developed shortness of breath, cough, and malaise, COVID-19 was suspected and PCR testing was positive. Examination was unremarkable except mild wheezing in the lower lung fields. He was afebrile with normal blood pressure and slight tachycardia and tachypneic. Pulse ox saturation on room air was 90%. His COVID-19 infection was treated with supportive care- cough suppressant, rest, hydration. He did not use any inhalers, tocilizumab, or steroids and did not require hospitalization or oxygen. His symptoms lasted about 2-3 weeks, before complete resolution. He was in his usual state of health for about 6 months, but developed mild left sided chest pain. EKG was unremarkable, however, Chest X-ray and subsequent Chest CT-Scan showed bilateral lower lobe lung masses. Patient underwent CT-guided biopsy of the right lung mass. Morphology of the sample showed a possible cryptococcal organism, but fungal culture was negative. Subsequent cryptococcus antigen test in serum was positive (titer 1:320). The patient's symptoms improved without any antimicrobial treatment. Because the patient did not feel ill anymore, he refused any treatment or further evaluation by an infectious disease specialist.

Discussion

Cases of opportunistic infection, especially cryptococcal species, have been reported in patients with COVID-19 infection. The possible mechanisms have been explained from a few different perspectives; viral infection factor, medication factor, and patient factor. One proposed mechanism is that there is an immune system change from immune dysregulation including T-cell lymphocytopenia caused by COVID-19 infection itself. Subsequently, deficiency in T-cell lymphocytes can make patients vulnerable to any opportunistic fungal infection, including cryptococcus.[1] Another is that increased dexamethasone use or immunosuppressive use, such as tocilizumab in management of COVID-19 can decrease lymphocyte proliferation and T cell activation causing dampening of the immune system.[2,3] The other focused on patient factors. One paper warns that, in COVID-19 patients, it is important to identify opportunistic fungal infection risk factors in advance, such as uncontrolled diabetes, history of using immunosuppressive agents, history of using high dose of steroid for long time, cirrhosis, or malignancy.[4]

Although it is rare to encounter cryptococcal infection in an immunocompetent patient with COVID-19, there are some cases reported in the literature. According to a case review, there were 18 cases of cryptococcal infection in patients with COVID-19.[5] Although the majority of patients were older adults with a few co-morbidities, only a few cases were immunocompromised patients at baseline.[5] Of note, the case review included two young patients in their 20's. However, one had human immunodeficiency virus (HIV) at baseline, and the other had autoimmune hemolytic anemia at baseline.[6,7] One case from South Korea was the most similar to our case.[1] The patient was healthy at baseline, and the disease severity was mild, limited to the pulmonary system. The timing of cryptococcus infection diagnosis was a few months after COVID-19 infection, which was similar to our case.[1] Notably, our patient has no known history of immune-compromising diseases or was never treated with any immunosuppressive agents in order to treat COVID-19 infection. Some researchers thought that severe viral infection may disrupt respiratory epithelium lowering local immunity, cause overexpression of anti-inflammatory cytokines, dysregulate T-helper cell differentiation, and impair cell-mediated immune response, making a host prone to fungal infection.[8,9] Actually, a multi-center study in Belgium and Netherlands found that severe influenza infection was an independent risk factor for a patient to have invasive aspergillosis (adjusted odds ratio 5.19; 95% CI 2.63-10.26; $p<0{\cdot}0001$).[10] In our patient, COVID-19 virus may have caused damage in the lining of the lung and caused opportunistic fungal infection.

Another interesting point to note was the timing of the fungal infection diagnosis. In many other reported cases, the diagnosis was made during the same admission for COVID-19 or post-mortem.[5] However, our patient was never admitted to the hospital, and cryptococcal antigen was identified several months after recovery from COVID-19. The patient may have been infected with cryptococcal pathogen during or sometime after COVID-19 infection, but the sequala of the fungal infection may have not been displayed until several months

later as he did not have any obvious neurological or pulmonological symptoms. One could argue that it could be a resolved infection with persistently elevated serum antigen based on the fact that he had a negative culture from the pulmonary masses, but had an elevated serum cryptococcal antigen. At this time, there is no valid analysis that shows a clear time frame of clinical/radiographical manifestations of pulmonary cryptococcal infection in an immunocompetent individual post COVID-19 infection.

In terms of management, antifungal monotherapy (fluconazole for several months) has been shown to be an effective treatment modality in pulmonary cryptococcal infection, but it was suggested that observation without initiating an antifungal agent could be considered in asymptomatic immunocompetent patients.[11,12] As in this case presented, post COVID-19 fungal infection is rare, but possible in a healthy, immunocompetent patient. Therefore, close follow-up for any new or persisting symptoms is essential even after full recovery from COVID-19.

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