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SARS-CoV-2 induced lymphopenia leading to novel PML infection

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Introduction

Lymphopenia has been correlated with severe Coronavirus disease 2019 (SARS-CoV-2) in the literature since the beginning of the pandemic (Huang and Pranata, 2020). Lymphopenia is defined as a lymphocyte count <1000 cells/μL and is related to a risk of poor clinical outcome (Huang and Pranata, 2020). Some of the clinical manifestations of SARS-CoV-2 infection have caught the attention of neurologists. The most common complaints currently reported have been headache and dysfunction of olfaction and gustatory sensation (Whittaker et al., 2020). Up until now, development of progressive multifocal leukoencephalopathy (PML) has mainly been associated with severe and prolonged immunosuppression (Sabath and Major, 2002). However, a recent patient case has compelled us to emphasize the importance of ruling out this rare central nervous system infection even if the only known immunocompromising risk factors is a history of SARS-CoV-2 infection.

PML is an opportunistic infection of the central nervous system caused by the JC virus (JCV). Although up to 80% of humans express serum antibodies to this virus, very few individuals develop PML (Weissert, 2011). The infection involves progressive damage of oligodendrocytes and can be fatal within months if not properly diagnosed and managed (Weissert, 2011). Symptoms of PML vary depending on the location and amount of cell damage. Patients commonly suffer from paralysis, seizure, loss of vision, and major neurocognitive deficits. There has been one case in the literature of worsening PML following SARS-CoV-2 pneumonia (Borrelli et al., 2021), but the patient had a history of multiple sclerosis and was already diagnosed with PML related to the patient's immunosuppressive medication natalizumab.

We present a novel case of SARS-CoV-2 induced lymphopenia which triggered new onset PML. This case is especially interesting to the neurological community because the patient had no prior history of immunodeficiency state or immunosuppression therapy. Through this report, we hope to bring attention to the unique impacts of the immunologic changes associated with SARS-CoV-2 infection and the risk they pose to patients for potential secondary opportunistic central nervous system infections.

Case description

A 64-year-old male presents with a four month history of progressive cognitive and physical neurologic decline. He had no significant past medical history prior to the initial start of his symptoms and was historically only on a multi-vitamin. He was found to have SARS-CoV-2 with very mild flu-like symptoms 4 weeks prior to the onset of his neurologic symptoms. Subsequently he started having subjective right sided weakness in his upper and lower extremity, mild language difficulty both in fluency and comprehension, difficulty completing tasks, and problems with concentration. Initially he was diagnosed with Post-COVID encephalitis undergoing a short trial of high dose steroids at an outside facility which did not improve his symptoms. He continued to clinically decline, eventually stopping work, with multiple falls, unable to walk without assistance, significant right sided weakness at 4-/5 in the upper and lower extremities, 3+ reflexes throughout, spasticity right worse than left, worsened language ability, withdrawn mood, and overall decreased ability to do instrumental activities of daily living requiring assistance from his significant other. At this point he was admitted to our inpatient facility.

His-basic blood work showed no significant signs of infection, normal total white blood cell count, but did show a grade 2 (per world health organization international classification criteria) lymphopenia with an

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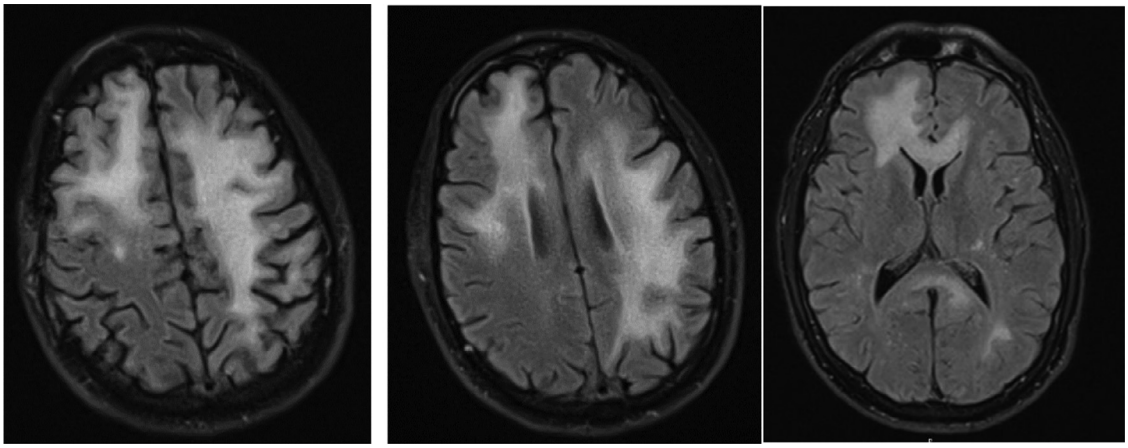

Fig. 1. Image of an MRI T2 sequence findings consistent with Progressive Multifocal Leukoencephalopathy.

	CD3 counts (cells/ μL)	CD4 counts (cells/ μL)	CD8 counts (cells/ μL)
Range	892-2,436	382-1,614	157-813
Baseline	141	81	52
30 days	253	143	93
60 days	272	137	114

Fig. 2. Summary of T-cell Lymphocytes over the course of management.

absolute count of 780 cells/ μL (normal >1000 cells/μL). The following biological studies were all normal: cytoplasmic neutrophil antibodies, ehrlichia antibodies, human immunodeficiency virus polymerase chain reaction (PCR), blood cultures, fungal cultures, herpes simplex virus PCR, flow cytometry, immunuloglobulin A, G, M, sedimentation rate, C-reactive protein, antinuclear antibodies, and SARS Cov-2 PCR. The only cerebral spinal fluid (CSF) study that was abnormal on the initial work-up was protein being slightly elevated at 64 (normal 15–45 mg/dL) and the following CSF studies were normal: 1 nucleated count, 0 red blood count, lactic acid, angiotensin converting enzyme, myelin basic protein, anti-amphiphysin, anti-AGNA-1, anti-ANNA-1, anti-ANNA-2, anti-ANNA-3, anti-CRMP-5-IGG, anti-PCA-TR, anti-PCA-1, anti-PCA-2, Anti-GAD, venereal disease research laboratory, oligoclonal bands, fungal cultures, tau protein, cytology, cryptococcal antigen and 14–3–3 protein assay. His-Magnetic Resonance Image (MRI) brain showed multifocal, confluent, subcortical white matter changes, involving bifrontal lobes, bilateral temporal lobes, left parietal and occipital lobes, and the corpus callosum as shown in Fig. 1. Given the characteristic imaging pattern JCV viral polymerase chain reaction (PCR) was sent in the CSF as well as obtaining a brain biopsy. The CSF viral PCR was qualitatively positive (no quantitative value available) and the brain biopsy was also consistent with JCV infection with the following characteristics: demyelination, atypical glial cells, reactive astrocytes and absence of any lymphocytic malignancy markers or malignant cell types, and no frank necrosis. There was no JCV PCR test ran on the brain tissue; however, based on the American Academy of Neurology PML diagnostic criteria (Berger et al., 9) using the combination of the clinical, imaging, and CSF findings this met criteria for definitive PML infection.

At this time a more exhaustive immunologic work-up was obtained which did show significant reduction in T cell lines, specifically CD3 at 141 cells/ μL (normal 892–2436 cells/ μL), CD8 at 52 cells/ μL (normal 157–813 cells/ μL) and CD4 at 81 cells/ μL (normal 382–1614 cells/ μL). The patient was treated with a 5 day course of intravenous immunoglobulins (IVIG), placed on mefloquine, and mirtazapine. He was unable to tolerate the mefloquine secondary to worsening psychosis and was also taken off mirtazapine due to the requirement of additional mood medications using valproic acid and quetiapine. After one month his T cell line was re-evaluated showing some improvement with CD3 at 253 cells/ μL, CD8 at 93 cells/ μL, and CD4 at 143 cells/ μL. The patient was then started on pegfilgrastim 6 mg for the promotion of immune reconstitution and continued on 28 day cycles of this medication. Subsequent T cell counts show CD3 at 272 cells/ μL, CD8 at 114 cells/ μL, and CD 4 at 137 cells/ μL. This lymphocyte data is summarized in Fig. 2. In addition to this reconstitution of his T cell line he is clinically improving, with improved movement on his right side, improved strength to 4+/5 in the upper and lower extremities, ambulating independently, more spontaneous conversation, oriented to person, place, time, and context, able to follow 2-step commands, improved attention, overall clinically improved, but still far from his baseline.

Discussion

This case highlights both the long term potential complications from SARS-CoV-2 infection as well as the secondary opportunistic infectious risk of development of Progressive Multifocal Leukoencephalopathy (PML). Although JCV exposure is common, patients having actual JCV infection is rare and are most commonly found in severely immunocompromised patients (Sabath and Major, 2002). SARS-CoV-2 infection has been associated with post-infectious lymphopenia, leading to an immunocompromised state (Huang and Pranata, 2020; Tavakolpour et al., 2020). The presence of decreased T cell lymphocytes in this patient is most likely related to his prior SARS-CoV-2 infection as the patient had no prior history of immunocompromised state, no prior history of repeated infections, and was negative for acute causes, mainly being HIV infection.

We believe this patient represents a novel clinical scenario in which SARS-CoV-2 infection was the only identifiable risk factors contributing to an immunocompromised state, which lead to a secondary opportunistic infection PML. Fascinatingly this patient had a relatively unremarkable SARS-CoV-2 infection, but the continued T cell lymphopenia highlights the challenges of chronic SARS-CoV-2 infection. PML is most commonly associated with known HIV infection, malignancy, and/or immunosuppression medication and is extremely unlikely to occur in patients that do not have immunocompromised status (Bharat et al., 2012). This patient was negative for HIV infection, no history of immunosuppression other than two courses of steroids that were initiated in response to the neurologic and imaging changes, no history of malignancy, organ transplant or underlying immunosuppressed state prior to SARS-CoV-2 infection. Although we do not have laboratory data on this patient prior to his course of high dose steroids, the steroids were only administered in response to the symptoms thus do not seem to explain the clinical progression of this patient. The patient saw clinical improve-

ment as his T cell lines appears to be recovering which could indicate better suppression of JCV and/or natural injury recovery. No additional JCV testing has been performed to better quantify this association as the patient desires to continue clinical monitoring and serial imaging as the primary means of assessment. It is hard to assess the clinical impact of the empirical pharmacologic agents, mefloquine and mirtazapine, used to treat PML as these were short trials secondary to the patient being intolerant of the side effects. It is hard to assess the natural history of immune recovery in SARS-CoV-2 induced lymphopenia as there is very little long term data, but in this particular patient our clinical goal was to attempt to improve immune reconstitution as best as possible with pegfilgrastim.

As observed with the monoclonal antibody natalizumab, which inhibits transmigration of T-lymphocytes into the CNS, this can allow JCV reactivation and replication which leads to a higher PML incidence (Lessons Learned From Progressive Multifocal Leukoencephalopathy Neurol Neuroimmunol Neuroinflamm Mar 2021). The most important immune cells in host defense against JCV appear to be T cells, which have been shown to decrease significantly in SARS-CoV-2 infection. This case highlights the importance of testing for JCV infection in patients with acute to subacute central nervous system injury presentations who have a history of SARS-CoV-2 infection, even if there are no other known risk factors for an immunocompromised state. Our goal is to increase awareness of the immunologic impacts of SARS-CoV-2 and the potential for secondary opportunistic infections, like PML which if diagnosed earlier can significantly prevent morbidity and potentially lower risk of mortality from this very difficult to treat CNS infection.

Declaration of Competing Interest

No conflicts to disclose for any authors.

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