The Connecting Link: A Case Report of the First Association of COVID-19 and Progressive Multifocal Leukoencephalopathy

Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus with diverse effects on the human body. Coronavirus disease 2019 (COVID-19) has been shown to produce some degree of immunosuppression in previously healthy hosts. This has been exemplified by the waves of mucormycosis that co-occurred alongside the pandemic. Studies have shown several pieces of evidence of dysregulation of immune responses among COVID-19 patients.[1] Progressive multifocal leukoencephalopathy (PML) is a neurological infection caused by the John Cunningham virus (JCV). The seroprevalence of JCV in the general population ranges from 39% in the younger population to 68% in the older population.[2] Yet, only a few of the many who harbor this virus happen to manifest the illness. The majority of cases of PML have been associated with human immunodeficiency virus (HIV) infection, immunotherapy for multiple sclerosis (MS), and lymphoproliferative and other immunodeficiency disorders. Herein, we report the first association of PML with COVID-19 and throw critical insights into the possible patho-mechanisms at play.

This 63-year-old gentleman, an agricultural worker, sustained COVID-19-related symptoms in the form of cough, shortness of breath, and sore throat 7 months back. He was tested positive for SARS-CoV-2 infection and treated symptomatically. Two weeks later, he developed foul-smelling blackish discharge from the nasal cavities, which was eventually diagnosed as mucormycosis of the nose and paranasal sinuses. He received medical treatment with amphotericin B and posaconazole for 2 weeks. Around 6 weeks after the onset of COVID-19, he started having recurrent daily fever spikes, which were followed 3 weeks later by a gradually progressive left hemiparesis that evolved over the next 6 months. This was accompanied by progressive behavioral disturbances manifesting as disinhibition, apathy, and executive dysfunction and formed visual hallucinations and severe insomnia. The patient was evaluated at this point of time. Clinical examination revealed a severely apathetic patient, with irrelevant speech, and doubly incontinent. He was not amenable to the assessment of higher mental functions. Motor examination revealed the paucity of movements of the left upper limbs. He had brisk muscle stretch reflexes, bilaterally extensor plantar response, and presence of release reflexes.

The patient's blood investigations, including complete hemogram, liver function test, serum electrolytes, vitamin B12, folate, and homocysteine levels, were normal. Serology for HIV, hepatitis B, and hepatitis C was negative. His serum CD4 count was low (344 cells/cu mm (500 to 1500 cells/cu mm)). The serum autoimmune encephalitis profile and paraneoplastic profile were negative. Cerebrospinal fluid (CSF) analysis showed no cells with normal glucose and protein. The CSF JCV polymerase chain reaction (PCR) was positive. Brain magnetic resonance imaging (MRI) revealed asymmetric (right > left) areas of T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity involving the subcortical white matter with the involvement of the U fibers of the right cerebral hemisphere and left frontal and parietal areas. The involvement of the right thalamo-capsular region and insula was also noted. The

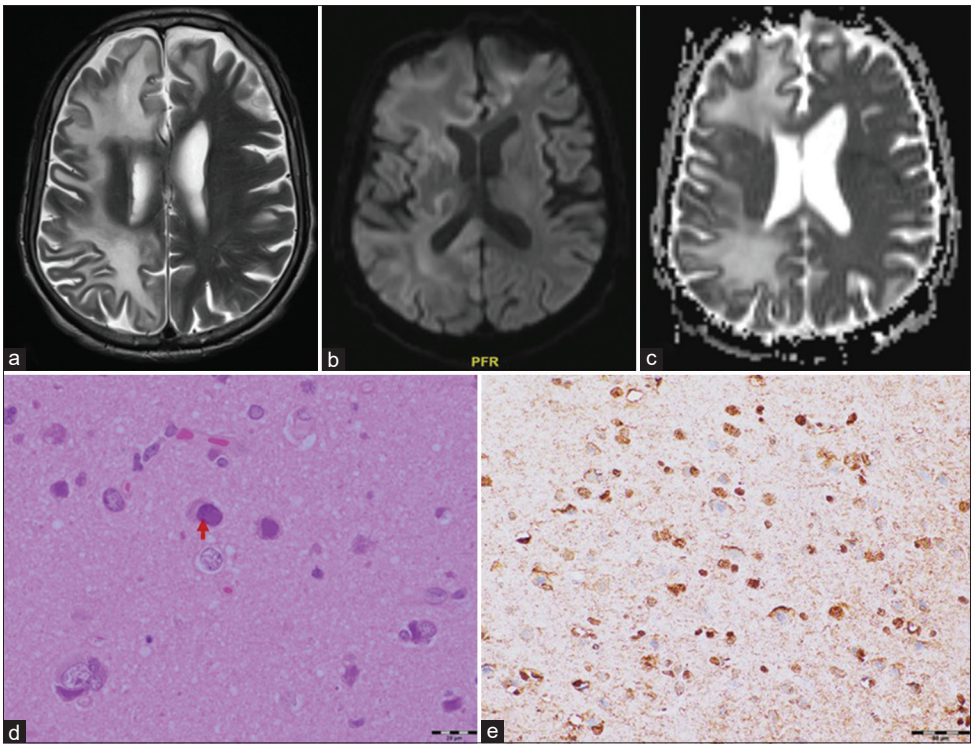

Figure 1: Brain MRI showing a) T2 axial showing asymmetric white matter tract hyperintensities right more than left with sparing of subcortical U fibers in the right cerebral hemisphere and left frontoparietal areas. b and c) Diffusion weighted imaging (DWI) and Apparent diffusion coeffiecient (ADC) axial sequence showing diffusion restriction along the leading edge of the lesion away from the cerebral cortex in the right cerebral hemisphere. d) Microphotograph showing oligodendroglial nuclear inclusions having a violaceous color (arrow) and e) SV40 immunostaining showing positively stained viral inclusions, consistent with JCV infection

leading edge of the lesion had signal changes away from the cortex with diffusion restriction. There was no contrast enhancement. The clinical–radiologic differentials considered were COVID-19-related leukoencephalopathy, PML, central nervous system (CNS) demyelination, and CNS lymphoma.

A brain biopsy revealed scattered oligodendroglia-like cells (round cells) with enlarged nuclei, showing homogenous amphophilic to pale eosinophilic inclusion admixed with a few scattered bizarre-looking astrocytes. Scattered and few loose aggregates of reactive microglial cells, along with reactive glial cells and subjacent parenchymal edema, were seen. Inclusion cells were positive for Simian virus (SV) 40 immunostaining. Thus, histological features were consistent with PML. He was offered treatment with the immune checkpoint inhibitor pembrolizumab, to which the patient's relatives did not give consent. T-cell adoptive transfer therapy could not be offered due to unavailability [Figure 1]. He was started on a trial of mirtazapine 15 mg/day along with supportive care and rehabilitation. During the hospital stay, he remained clinically status quo. Thereafter, he was lost to follow-up.

Discussion

Previous studies have shown the association of severe COVID-19 illness with lymphopenia, especially involving CD4+ T cells.[3] A multitude of pathophysiological mechanisms has been postulated. COVID-19 has been postulated as a trigger for pro-inflammatory cytokine storm involving massive release of tumor necrosis factor (TNF)-alpha and interleukin (IL)-6.[4] In particular, IL-6 has been shown to induce extrinsic apoptotic activity in the T cells, which, in turn, impairs the cytotoxic activity of CD8 and natural killer (NK) cells. This altered cytokine milieu starts interfering with the expansion and proliferation of T cells. Studies have revealed the downregulation of certain genes that aid in the activation, differentiation, and survival of T cells, namely, Mitogen-Activated Protein Kinase Kinase 7 (*MAP2K7*) and Son of sevenless homolog 1 (*SOS1*). In another postulated model, COVID-19 has been shown to lead to exhaustion of T cells, mediated by programmed cell death protein 1 (PD-1) and T-cell immunoglobulin and mucin domain 3 (TIM-3).[5]

Almost half of the adult population worldwide is infected with the nonpathogenic archetype of JCV,[6] acquired mostly through contaminated food and water. Primarily, it gets harbored in the tonsils and disseminated throughout the body via B cells.[7] However, in immunocompetent individuals JCV undergoes a period of dormancy. In the setting of impaired CD4+ and CD8+ T-cell function, the nonpathogenic JCV uninhibitedly replicates and forms neuropathogenic prototypes, which replicate and transform in the bone marrow and the brain.[8] The virus then infects the cortical gray matter and several other parts of the CNS. It has been observed that there is an independent

association of T-cell deficiency with the development of PML. Natalizumab is a key immunosuppressant used in the treatment of MS. However, it does not affect the CD4+ T cell count. Incidence of PML was similar on comparison of a cohort of MS patients on natalizumab for 4 to 6 years vs HIV-positive patients with a CD4 count of <200 cells/cu mm of blood for 5 years.[9] In addition, there have been reports of MS patients developing PML while on dimethyl fumarate therapy, in the backdrop of long-standing lymphopenia.[10] From the current literature, it may be inferred that low CD4+ cell counts were probably the underlying mechanism that led to the development of PML in our case. Our case represents the first in the literature, which have shown the unique connection between COVID-19 and PML, connected by lymphopenia. It adds yet another dimension to COVID-19. It is important to consider this differential in the appropriate clinical–radiological setting to avoid inadvertent delay in diagnosis, prevent inappropriate management with immunosuppressants, and convey appropriate prognostication to the patient's relatives.

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Conflicts of interest

There are no conflicts of interest.

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