Aseptic Meningitis after Recovery from SARS-CoV-2 in an Allogeneic Stem Cell Transplant Recipient

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ABSTRACT: SARS-CoV-2 emerged as a worldwide pandemic in late 2019 and initially was described as a primary respiratory illness. The clinical manifestations of COVID-19 are now known to encompass nearly all organ systems, including the central nervous system. We present a case of an allogeneic hematopoietic stem cell transplant recipient who recovered from documented SARS-CoV-2 infection and later presented with symptoms of meningitis. While cerebrospinal fluid analysis did not reveal any bacterial or viral etiologies, evidence of an inflammatory state, including ophthalmologic findings of episcleritis, indicate what is likely the first reported case of aseptic meningitis associated with SARS-CoV-2 infection after initial clinical recovery.

KEYWORDS: Meningitis, coronavirus, COVID-19, SARS-CoV-2, allogenic stem cell transplant

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel RNA coronavirus that emerged in December 2019 in Wuhan, China, and quickly became a worldwide pandemic.1 Early diagnostic strategies focused on respiratory manifestations, including, but not limited to, cough, sore throat, pneumonia, and flu-like symptoms, as well as other systemic symptoms including gastrointestinal symptoms and cardiac and renal failure.2-4 More than one-third of infected patients present with neurologic symptoms such as headache, dizziness, hypomnia, dysgeusia, and stroke, either ischemic or hemorrhagic.5 Critical cases lead to shock and multiorgan failure, with mortality reported to be at least 2% to 5%, depending on patients’ coexisting medical conditions, including immunocompromised status.6 While data is limited in patients after hematopoietic stem cell transplantation, there are indications that over half of patients with hematologic malignancies or other hematologic disease are likely to develop acute respiratory distress syndrome (ARDS) after infection with SARS-CoV-2 requiring mechanical ventilation, and critical events occurred in 32% of cellular therapy patients with 30-day overall survival of 78%.7,8 The significant neuroinvasive potential of SARS-CoV-2 has been postulated based on previous animal and human studies of SARS-CoV and MERS-CoV, and autoimmune mechanisms due to molecular mimicry between neuronal and viral proteins may also play a crucial role in the neurologic manifestations of coronavirus disease (COVID-19).9-12 Here we present a unique case of meningitis presenting after documented SARS-CoV-2 infection, without any causal bacterial, viral, or fungal pathogen identified, and subsequent resolution in an allogeneic stem cell transplant recipient.

Case Presentation
Our patient is a 32-year-old Nicaraguan female diagnosed with sickle cell disease (HgbSS) as a child, complicated by frequent vaso-occlusive crises including 2 myocardial infarctions and bilateral avascular necrosis of the knees. Approximately 18 months prior to this presentation, patient underwent allogeneic hematopoietic stem cell transplant (allo-HSCT) from her brother (10/10 match) after myeloablative conditioning with fludarabine, busulfan, and rabbit anti-thymocyte globulin. Immediate post-transplant course was notable for suspected graft-versus-host disease (GVHD), manifesting as mucositis, transaminitis, perineal ulcer formation, diarrhea, and left arm skin nodules (although skin biopsy was negative), for which she received a short course of steroids and methotrexate and tacrolimus for prevention of further GVHD. Patient was also started on levetiracetam and anti-hypertensive medications for hypertension and donor chimerism was 97.8% at day +365. Patient continued maintenance immunosuppression with gradually decreasing doses of tacrolimus and acyclovir. The most recent absolute CD4 count, about 2.5 months prior to presentation, was 502 cells/μL (normal 490-1749 cells/μL). Our patient presented in late April 2020 (day +505) with 4 days of fever, generalized headaches, neck pain without measurable increase in WBC count to presentation, was 502 cells/μL (normal 490-1749 cells/μL).
stiffness, pleuritic chest pain, non-productive cough, myalgias, nausea, vomiting, and diarrhea. At time of initial presentation to the emergency room, patient was afebrile with normal vital signs. Labs were notable for elevated pro-calcitonin (0.122 ng/mL, normal <0.08 ng/mL) with normal lactate and white blood cell count, and a nasopharyngeal swab PCR test positive for SARS-CoV-2. Chest X-ray was negative for acute pathology, and patient was discharged home with an albuterol inhaler, a 5-day course of azithromycin, and a 14-day course of hydroxychloroquine, while tacrolimus was discontinued. At this time, conclusive data was not available regarding the efficacy of hydroxychloroquine, remdesivir, and dexamethasone in the management of COVID-19. She continued to feel ill, with a fever at home of 39°C and continued diarrhea, nausea, vomiting, non-productive cough, and myalgias. While her clinical condition improved, a second nasopharyngeal PCR test for SARS-CoV-2 showed persistence of the virus, 20 days after the initial test. Patient reported resolution of symptoms at 34 days from first symptom, and 2 subsequent nasopharyngeal PCR tests for SARS-CoV-2, 34 and 38 days after initial positive test, were negative.

Approximately 2 months after initial symptom onset, our patient reported the recurrence of headaches with associated fever (measured as 102°F at home), chills, conjunctival injection, myalgias, nausea, vomiting, and diarrhea. On presentation to the emergency room, she was noted to be hypotensive (blood pressure 95/64 mm Hg), but afebrile and not tachycardic. Labs were notable for leukocytosis of 14.1×10^9/μL (normal 4.0-10.5×10^9/μL) with 58% neutrophils and 31% lymphocytes, elevated pro-calcitonin (0.106 ng/mL, normal <0.08 ng/mL), elevated C-reactive protein (2.5 mg/dL, normal 0-0.5 mg/dL), elevated ferritin (4548 ng/mL, normal 13-150 ng/mL), and mild elevation of alanine aminotransferase (43 U/L, normal 0-33 U/L) and alkaline phosphatase (195, normal 35-130 U/L) with normal aspartase aminotransferase. Chest X-ray showed a hazy opacity in the left mid- and lower lung zones, concerning for developing consolidation. Computed tomography (CT) scan of the brain demonstrated no acute pathology. SARS-CoV-2 testing via nasopharyngeal swab PCR was negative on presentation to the emergency room as well as a repeat test for SARS-CoV-2. Chest X-ray was negative and acid-fast bacilli (AFB) smear and culture were negative. Of note, Epstein-Barr virus (EBV) DNA was detected in CSF (227 IU/mL) with concurrent blood levels of 2200 IU/mL, in setting of known chronic EBV viremia with levels 4 months prior of 2800 IU/mL. Patient was afebrile on presentation but developed a fever on day 2 of admission with maximum temperature of 38.8°C. Patient continued to be febrile despite empiric antibiotic therapy, and intravenous ampicillin was added due to concern for *Listeria* given history of consumption of unpasteurized dairy products. Patient improved clinically and acyclovir was discontinued due to low concern for HSV. A stool viral PCR panel was ordered due to mild diarrhea, and no WBC, rotavirus, Norwalk virus, or *Clostridium difficile* toxin was detected. Additionally, a respiratory viral panel was negative for adenosivirus, enterovirus, rhinovirus, *non-SARS-CoV-2* coronavirus, metapneumovirus, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and multiple strains of respiratory syncytial virus, influenza, and parainfluenza. Vitamin B12 and folate levels were normal and human immunodeficiency virus (HIV) serology was negative.

While patient improved clinically neurologically, she continued to experience headaches and developed episcleritis, for which she was evaluated by ophthalmology and managed symptomatically with lubricant ophthalmic ointment. She underwent a second lumbar puncture 1 week after initial presentation, which demonstrated 12 WBCs/mm³, with 91% lymphocytes, 1% neutrophils, and 8% monocytes, normal glucose (54 mg/dL), and normal total protein (25 mg/dL). A second meningoencephalitis panel, with the addition of PCR testing for *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, CMV, enteroviruses, HSV-1 and -2, HHV6, varicella zoster virus (VZV), human parechovirus, and *Cryptococcus neoformans/gattii*, was also negative. JC virus DNA was negative and acid-fast bacilli (AFB) smear and culture were negative as well. Additional tests for Zika virus nucleic acid in the blood and urine and *Leptospira* and adenosivirus DNA in the CSF were also negative; and neither EBV DNA nor SARS-CoV-2 RNA (not tested previously) were detected in the CSF. Treponemal serology, (1-3)-β-D-glucan and galactomannan were undetectable in the serum. External laboratory studies demonstrated 3 paired bands were detected in both the CSF and serum, indicating the presence of an immune response to an inflammatory process outside the CNS.

Magnetic resonance imaging (MRI) of the brain was unremarkable. MRI angiogram of the head showed no evidence of a cerebral venous sinus thrombosis but did incidentally demonstrate a 3.4 mm saccular aneurysm projecting from the proximal segment of the right internal carotid artery. Neurology did
not feel this aneurysm was contributing to the patient’s symptoms and planned to follow with serial MRIs in the outpatient setting. Patient continued to demonstrate clinical improvement and was eventually discharged 11 days after presentation; she has since returned to her baseline. At her last routine post-transplant visit 45 days after her initial presentation, her immune status was reassessed; serum Ig level was 1531 mg/dL, absolute CD4+ T cell count of 610 cells/mm³, absolute CD8+ T cell count of 394 cells/mm³, and absolute CD19+ count of 892 cells/mm³. Patient provided written informed consent for publication of deidentified patient information.

**Discussion**

In this case, we demonstrate a rather unique presentation of aseptic meningitis occurring several weeks after symptomatic infection with SARS-CoV-2 with subsequent resolution of symptoms and of viral replication. In addition to several of the more common manifestations of SARS-CoV-2 infection, our patient also presented with headaches, one of the most common neurologic symptoms, present in 8% to 13% of infected patients.14-16 It is important to note that at the time of presentation for suspected meningitis and throughout the course of treatment, our patient tested negative multiple times via nasopharyngeal PCR testing, and SARS-CoV-2 was not isolated in the CSF; in fact, nearly all testing for viral and bacterial culprits of meningitis was unrevealing aside from low-level detection of EBV in the setting of known chronic EBV viremia. In addition, drug-induced aseptic meningitis (DIAM) was of low likelihood in this case given the lack of use of common drugs which have been associated with DIAM prior to this patient’s presentation, including immunosuppressive agents like intravenous immunoglobulin, non-steroidal anti-inflammatory drugs, and antibiotics such as trimethoprim-sulfamethoxazole, ciprofloxacin, and metronidazole.15-17 However, the presence of paired oligoclonal bands detected simultaneously in the serum and CSF in the setting of neurological symptoms signifies a systemic inflammatory state with concurrent or secondary central nervous system involvement in our patient.18 Moreover, the development of episcleritis, typically self-limiting and often associated with viral infections, indicates a likely chronic inflammatory state induced by our patient’s recent infection with SARS-CoV-2. Two cases to date have described episcleritis in connection with SARS-CoV-2 infection, either as a presenting symptom with later development of fever and respiratory symptoms19 or after the onset of systemic symptoms.20

Immunocompromised patients, in particular allo-HSCT recipients, are at significant risk of CNS infections and can manifest with more nonspecific symptoms and may present with attenuated inflammatory responses.21 HHV-6 is the most common viral etiology of encephalitis following allo-HSCT, typically presenting with seizures or loss of consciousness, with MRI enhancement observed in the limbic system.22,23 Other viral CNS infections described in allo-HSCT recipients include HSV, CMV, VZV, EBV, JC, and adenovirus, all of which were excluded in our patient.24-29 There is some evidence of the likely neurotropic nature of SARS-CoV-2, as SARS-CoV has been detected in the CSF and brain tissue; however several recent case reports associating SARS-CoV-2 infection with stroke and acute hemorrhagic necrotizing encephalopathy without CSF findings indicate that either SARS-CoV-2 does not cross the blood-brain barrier or does not require direct infiltration for pathogenesis, instead acting to create intracranial cytokine storms or procoagulant states.30-33 To date, nearly 60 case reports or series have described viral meningitis or meningooencephalitis associated with SARS-CoV-2 infection with only 13 patients demonstrating positive RT-PCR for SARS-CoV-2 in the CSF. Many of these reports have noted a discordance between serum and CSF positivity, and in several cases, CSF samples were unable to be tested for SARS-CoV-2, as is the case with our patient.34-42 In fact, studies of systematic screening of CSF in patients with SARS-CoV-2 with neurologic manifestations suggest that CSF positivity is irrelevant, considering contamination by blood while CSF is being obtained, kinetics of clearance of the virus depending on symptom severity at time of specimen collection, or sensitivity of molecular testing, which has rapidly evolved during this pandemic.31,43,44

Molecular mimicry in the Coronaviridae family was first described in 1995, specifically with the S protein of bovine coronavirus and the Fc gamma receptor, and subsequently with human coronavirus strain 229E and myelin basic protein, and was postulated as a mechanism for viral pathogenicity in the wake of the severe acute respiratory syndrome (SARS) outbreak in 2003.45 Similar proposals have emerged to implicate molecular mimicry with proteins involved in the olfactory system, differentiation of B cells and macrophages, and function of endothelial cells as potential mechanisms for anosmia, leukopenia, and multi-organ failure secondary to vascular damage seen with COVID-19.46 Molecular mimicry may well be induced in SARS-CoV-2 infections in the setting of stress responses in endothelial cells and subsequent dysfunction and respiratory regulation by the brainstem.47 Furthermore, the identification of more than 30 distinct peptides identical between SARS-CoV-2 and the human proteome, 20 of which were not previously observed with other coronavirus strains, provides a basis for host-pathogen molecular mimicry contributing to the pathogenesis of COVID-19, especially considering enrichment of mimicked peptides in lung, trachea, esophagus, myocytes, intestines, pancreas, macrophages, fibroblasts, and smooth muscles cells in large arteries such as the aorta.48 In addition, heptapeptide sharing has been identified between the SARS-CoV-2 spike glycoprotein and surfactant-related proteins.49,50 Molecular mimicry may well play a role in neurologic manifestations after acute SARS-CoV-2 infection by nasopharyngeal testing without concomitant CSF positivity, including Guillain-Barre syndrome or polyradiculoneuropathy and myasthenia gravis.51-54 The implications for molecular recognition of viral antigens in the CNS, both cellular and humoral responses, need further investigation.
mimicry as a potent mechanism by which SARS-CoV-2 can evade the immune system (by exploiting recognition as a host peptide) and/or elicit autoimmune dysfunction must be considered in the absence of documented active infection, and further studies are certainly necessary to elucidate the relevance of molecular mimicry or other autoimmune phenomena in the pathogenesis of SARS-CoV-2.

Author Contributions
FB, LJL, and DLP created the concept of this manuscript. FB wrote manuscript with assistance of all authors. All authors contributed to the final version of the manuscript.

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