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Mild COVID-19 infection despite chronic B cell depletion in a patient with aquaporin-4-positive neuromyelitis optica spectrum disorder.

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus SARS-CoV-2, which affects the lung and other organs. After an incubation period of 3-14 days, the infection presents with symptoms of variable severity, from mild flu-like disease to severe pneumonia and cytokine storm with increased mortality. Immunocompromised patients may have higher risk of adverse outcomes; hence, there is an urgent need to evaluate the immune response and clinical outcomes of SARS-CoV-2 infection in these patients. Here, we report a 59-year-old woman with aquaporin-4-positive (AQPR4+) neuromyelitis Optica treated with rituximab who developed mild respiratory symptoms with COVID-19, despite B cell depletion at the time of infection.

Introduction

SARS-CoV-2, a novel coronavirus that originated in Wuhan, China, has produced a global pandemic known as COVID-19 with substantial mortality and morbidity (Guan et al., 2020). To infect the host, SARS-CoV-2 uses the viral receptors ACE2 and TMPRSS2, which are membrane-associated proteins expressed in many cells throughout the body, particularly the respiratory system (Hoffmann et al., 2020). Knowledge about the immunopathology of COVID-19 is evolving, and there is heterogeneity of symptoms among the affected population. Most cases are mild, but in a number of patients, the disease evolves into an acute respiratory distress syndrome (ARDS) (Wu et al., 2020) or a dysregulated immune system state leading to cytokine storm, most often in older adults, requiring intensive care and resulting in increased mortality (Mehta et al., 2020). There is growing evidence that some younger patients may have worse outcomes as well, which may be related to host factors, including an altered immune system, genetics, and comorbidities like obesity and smoking (Guan et al., 2020). Based on these observations, there is concern that patients treated with immunosuppressive drugs may be at a higher risk of developing poor outcomes during a SARS-CoV-2 infection. Therefore, there is great interest in determining the impact of COVID-19 in patients on disease-modifying therapies (DMTs) for autoimmune neurological diseases like multiple sclerosis (MS), neuromyelitis Optica spectrum disorder (NMOSD) and others. An important concern is how B cell depletion modifies the host ability to mount an effective response to SARS-CoV-2. Here, we describe an AQPR4+ NMOSD patient treated with rituximab who developed mild COVID-19 infection despite B cell depletion. We also discuss the emergent evidence of the host cellular and humoral immunity against SARS-CoV-2.

Case report

This report was considered exempt research by the UConn Health IRB. A 59-year-old woman presented with transverse myelitis in 2006 and was initially diagnosed with multiple sclerosis (MS). She had subsequent relapses with optic neuritis in each eye separately and once simultaneously. MRI of the spine and brain in 2017 showed a left-sided long segment cord signal abnormality extending from C2 to C6 with associated mild cord atrophy, stable since 1 year prior, stable short segment myelitis of the thoracic cord at the level of T2-T3 without evidence of restricted diffusion or abnormal enhancement, and multiple small foci of T2/FLAIR signal hyperintensity within the cerebral white matter bilaterally. She was recategorized in 2014 as NMOSD, AQPR4-positive based on white matter disease in the brain, longitudinal transverse myelitis in the cervical spine, and positive serology for AQPR4 antibody (Fig. 1A, B). She was initially started on azathioprine, then transitioned to rituximab in early 2014 resulting in chronic B cell...
and told her to continue Tami postnasal drip. She was afebrile. Her PCP diagnosed acute viral sinusitis spiratory status. On day 28, she developed sinus congestion with
dyspnea. She presented to the emergency department, where she was
tachycardic with a temperature of 100.4 °F, and O2 saturation was 94%
and her presentation. During the COVID19-positive phase of her illness, she
did not present any new neurological signs or symptoms and there was
a suggestion that in some patients the severe disease is due to
immune dysregulation, in particular, cytokine storm, therefore tar-
getting cytokines such as IL6 can be beneficial (Mehta et al., 2020). This
suggestion is supported by reports of cases of mild disease in a patient
with long term corticosteroid use (Han et al., 2020) but there is a need
for prospective randomized trials to determine if immunosuppression or
immunomodulation may be protective from worse outcome of COVID-
19.
The impact of Immunosuppressive medications on the course of
COVID-19, especially DMTs like rituximab that deplete circulating B
cells, is of particular concern. There are reports of severe and even fatal
viral infections in patients on rituximab. These include encephalitis due
to Coxsackie A16, Enterovirus (Sham et al., 2019) (Kassab et al.,
2013), Powassan (Solomon et al., 2018), Tick-Borne Encephalitis
(Steininger et al., 2017), West Nile (Morjaria et al., 2015), JCV neu-
rological disease including PML (Ishikawa et al., 2018) (Berger et al.,
2018) and granule cells neuronopathy (Dang et al., 2014). Our patient
did not present any new neurological signs or symptoms and there was
no indication for a lumbar puncture. Currently, it is unclear if SARS-
CoV-2 is neurotropic. The SARS-CoV-2 receptors ACE and TMPRSS2
are not highly expressed in the brain, although preliminary evidence from
single cell RNA sequencing data suggest that the olfactory epithelium
expresses these receptors. This may explain the cases of anosmia seen in
COVID-19. There is preliminary evidence that oligodendrocytes may
express COVID receptors, and recently there was a case of encephalitis
with SARS-CoV-2 found in the CSF (Moriguchi et al., 2020). Moreover,
neuropathy of coronaviruses may be independent of the expression of
viral receptor in brain cells (Weiss, 2020). Other neurotrophic cor-
ronaviruses use different receptors to cause disease in im-
munosuppressed patients. Our patient had no encephalitic symptoms
and was negative for metapneumovirus, which can cause severe en-
cephalitis. (Bohmwald et al., 2018)

Discussion
Our patient had a prolonged flu-like illness that was either a pro-
longed course of COVID-19 or more likely a different viral respiratory
infection followed by SARS-CoV-2. We cannot distinguish between
these two possibilities since she was not tested for SARS-CoV-2 early in
her presentation. During the COVID19-positive phase of her illness, she
had only mild respiratory symptoms with moderate constitutional
symptoms. She did not develop overt respiratory insufficiency and
changes in the chest X-ray were mild, with minimal lab abnormalities.
She had severe lymphopenia that recovered (Fig 1E), indeed the re-
appearance of CD8+ T cells precede the resolution of symptoms and is
consistent with an effective immune response to SARS-CoV-2 in non-
severe cases. (Irani Thavaranjan et al., 2020) Lymphopenia is seen fre-
frequently, and recent work suggests that sustained lymphopenia, espe-
cially CD8+ T cells is an independent predictor for COVID-19 severity
(Wang et al., 2020) Her neutrophil population (ANC) increased at the
time of increased disease severity, and then declined as her lymphocyte
population partially recovered (Fig 1C). The ratio of ANC/ALC has been
suggested as a readily available marker of disease severity in COVID
infection (Lagunas-Rangel, 2020).

There is a suggestion that in some patients the severe disease is due
to immune dysregulation, in particular, cytokine storm, therefore tar-
getting cytokines such as IL6 can be beneficial (Mehta et al., 2020). This
suggestion is supported by reports of cases of mild disease in a patient
with long term corticosteroid use (Han et al., 2020) but there is a need
for prospective randomized trials to determine if immunosuppression or
immunomodulation may be protective from worse outcome of COVID-
19.
patients to mount an effective humoral and cellular immune response to an infection of SARS-CoV-2 or to a future COVID-19 vaccine (Yri et al., 2011).

In summary, our patient developed only a mild course with COVID-19 despite B cell depletion and may be instructive regarding the behavior of SARS-CoV-2 infections in patients with immunomodulation. Long term prospective studies are needed to examine the role of B cells on the immune responses against emerging or endemic human coronaviruses (Weiss, 2020), including SARS-CoV-2.

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