Early SARS-CoV-2-associated acute transverse myelitis: A case for neurotropism?

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There are increasing reports of immune-mediated and para-infectious syndromes beyond the well-known respiratory manifestations of severe-acute-respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, the spectrum of severe neurological sequelae of SARS-CoV-2 remains undefined. We present the case of a 66-year-old female with rapidly progressive lower limb neurology 3 days post SARS-CoV-2 infection. Clinical and radiological findings were in keeping with transverse myelitis and treatment success was achieved with methylprednisolone and remdesivir. This report will discuss the associations between SARS-CoV-2 and acute transverse myelitis. We believe this is one of few described cases of early SARS-CoV-2-associated transverse myelitis secondary to neurotropism and the first successfully treated with the inclusion of remdesivir in the therapeutic regimen.

Keywords: COVID-19, myelitis, neurotropism, SARS-COV-2

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe-acute-respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is now in its third year. There is a large body of evidence describing neurological manifestations of SARS-CoV-2, such as headache, dizziness, anosmia and neuralgia [1]. However, neurological disorders of greater consequence such as meningoencephalitis, myasthenia gravis, Guillain–Barre syndrome and acute transverse myelitis (ATM) remain relatively undefined. The underlying mechanism of such neurological sequelae can be categorised into three main groups. The first, a result of the systemic inflammatory response syndrome and multi-organ failure. The second, direct SARS-CoV-2 viral invasion and infection of the central nervous system (CNS), that is, neurotropism and third, postinfectious immune-mediated neurological syndromes [2, 3].

ATM is a rare, acquired inflammatory disorder of the spinal cord with an incidence of up to three per 100,000 patient-years [4]. ATM presents with rapid onset of weakness, sensory disturbances and bowel or bladder dysfunction. ATM can occur due to infection, paraneoplastic processes, systemic inflammatory diseases or as a continuum of neuroinflammatory CNS disorders. Para-infectious ATM is common, whereby pathogenesis is due to the systemic response to infection rather than direct microbial infection itself [4].

The current literature primarily describes transverse myelitis occurring late in SARS-CoV-2 infection or the postinfectious period, consistent with immune-mediated pathogenesis. We present a case of ATM occurring early in the illness course, a neurological manifestation perhaps representing neurotropism with direct CNS infection. To our knowledge, this is the first case report of remdesivir use in the treatment regimen for SARS-CoV-2 ATM. Here, we discuss the clinical course, possible pathophysiological mechanisms and briefly review the literature on SARS-CoV-2 ATM.

Case

A 66-year-old female presented to the emergency department with acute onset of progressive ascending bilateral lower limb paraesthesia over 12 h, associated with gait ataxia and a sensation of urinary retention. She described having a sore
throat and cough in the preceding 3 days. The patient’s medical history included hypercholes-
terolaemia and acne, managed with rosuvastatin
and isotretinoin, respectively. A local small business
owner, she emigrated from Vietnam to Australia in the 1990s and last travelled overseas
3 years prior. She had not been diagnosed with
COVID-19 prior to this presentation nor experi-
enced any recent respiratory or gastrointestinal
illness. She received two doses of the ChAdOx1
nCoV-19 vaccine, with her second dose 4 months
prior to this presentation.

On initial examination, she was alert, with a Glas-
gow Coma Score of 15, pulse oximetry above 95% on room air and temperature 36°C and was haemo-
dynamically stable.

The patient could ambulate, and a neurological
examination revealed lower limb weakness with
Medical Research Council (MRC) scores of 4/5 at
the hip and 5/5 in the distal lower limb, bilaterally.
Sensory perception to touch was reduced in all der-
matomes of the lower limbs. Deep tendon reflexes
were preserved at the knee and ankle. Upper limb
neurological exam was unremarkable.

Six hours following hospital admission, her weak-
ness had progressed to a 3/5 MRC score at
the hip and knee and 4/5 at the ankle bilat-
early. Ankle reflexes were now reduced bilat-
erally with an equivocal Babinski reflex. There was
hypoesthesia towards noxious stimuli, more pro-
nounced within the right lower limb and up to the
abdomen corresponding to the T10 dermatome.
She was now unable to ambulate independently.
Peak flow measurements were 300–350 L/min
repeatedly.

Nasopharyngeal SARS-CoV-2 polymerase chain
reaction (PCR) confirmed COVID-19 with cycle
threshold values of 15.3 and 15.8 on a TaqPath
COVID-19 assay. A respiratory viral multiplex PCR
was negative. Preliminary biochemistry was unre-
markable and there was no evidence of an acute
inflammatory response, with C-reactive protein
(CRP) within normal limits. Autoimmune markers
were later tested and negative (Table 1). A lumbar
puncture was performed with an opening pressure
of 19 cm of water. Cerebrospinal fluid (CSF) pro-
tein measured mildly high 0.54 g/L, and leucocyte
cell count was 8 × 10⁶/L. No organisms were seen
on gram stain, and cultures remained negative.
CSF PCR testing for Herpesviridae, enterovirus,

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Table 1. Laboratory findings

| Full blood count                  | Result | Reference range |
|----------------------------------|--------|-----------------|
| Haemoglobin (g/L)                | 140    | 115–165         |
| Leucocyte count (× 10⁶/L)        | 7.2    | 4.0–11.0        |
| Neutrophil count (× 10⁹/L)       | 4.7    | 2.0–8.0         |
| Lymphocyte count (× 10⁹/L)       | 2.1    | 1.0–4.0         |
| Platelet count (× 10⁹/L)         | 218    | 150–450         |

| Biochemistry                     |        |                 |
|----------------------------------|--------|-----------------|
| CRP (mg/L)                       | <2.9   | <3.0            |
| CK (U/L)                         | 101    | <161            |
| TSH (mIU/L)                      | 2.78   | 0.4–4.0         |
| Vitamin B12 (pmol/L)             | 614    | >180            |
| Folate (nmol/L)                  | 38.6   | >10.0           |
| Creatinine (umol/L)              | 72     | 45–90           |
| eGFR (ml/min/1.73 m²)            | 76     | >90             |
| APTT (s)                         | 26.3   | 23.0–35.0       |
| PT (s)                           | 10.3   | 9.0–13.0        |
| INR                              | 0.9    | 0.8–1.2         |
| Fibrinogen (g/L)                 | 3.4    | 2.0–4.0         |
| Bilirubin (umol/L)               | 8      | <25             |
| ALP (U/L)                        | 92     | 40–130          |
| GGT (U/L)                        | 42     | <51             |
| AST (U/L)                        | 30     | <41             |
| ALT (U/L)                        | 39     | <41             |
| Hepatitis B sAg                  | Not detected |
| Hepatitis B sAb (IU/L)           | 130    |
| Hepatitis B cAb                  | Not detected |
| HIV Ag/Ab                        | Not detected |
| T. pallidum IgG                  | Negative |
| Mycoplasma IgG                   | Negative |
| Mycoplasma IgM                   | Negative |
| HTLV1 Ab                         | Not detected |

| Autoimmune/screen               |        |                 |
|----------------------------------|--------|-----------------|
| c-ANCA                           | Negative |
| p-ANCA                           | Negative |
| ANA titre                        | <160   | <160            |
| anti-SS-A Ab                     | Negative |
| anti-SS-B Ab                     |         |
| anti-RNP Ab                      |         |
| anti-topoisomerase 1 Ab          |         |
| anti-Jo 1Ab                      |         |
| anti-PCNA Ab                     |         |

(Continued)
Table 1. (Continued)

| Autoimmune/screen             |
|-------------------------------|
| anti-ribosomal P Ab           |
| anti-PM/SCL Ab                |

Abbreviations: Ab, antibody; Ag, antigen; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibody; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; cAb, core antibody; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; HTLV1, human T-lymphotropic virus 1; INR, international normalised ratio; PCNA, proliferating cell nuclear antigen; PM-SCL, polymyositis/scleroderma; PT, prothrombin time; ribosomal P, ribosomal protein; RNP, ribonuclear protein; sAb, surface antibody; sAg, surface antigen; SS-A, Sjögren’s syndrome related antigen A; SS-B, Sjögren’s syndrome related antigen B; T. pallidum, Treponema pallidum; TSH, thyroid stimulating hormone.

Flavivirus and SARS-CoV-2 were negative. Anti-neuromyelitis optica antibody and oligoclonal bands were negative.

Suspecting myelopathy, an magnetic resonance imaging (MRI) spine was pursued that identified T2 signal hyperintensity on the left side of the cord at the level of T10, with subtle patchy T2 signal changes within the cord from T11 to T12 (Fig. 1). MRI brain was unremarkable.

The diagnosis of acute T10 transverse myelitis was made, and the patient was commenced on 1 g of intravenous (IV) methylprednisolone for 3 days and loaded with 200 mg IV of remdesivir, followed by 100 mg IV daily to complete a 5-day course. In this instance, approval for off-label use of remdesivir was sought, and the patient provided her consent for treatment. There was a steady clinical improvement over 7 days, and the patient was able to

![Fig. 1](image-url)
ambulate unaided by day 7. The patient was subsequently placed on a weaning dose of oral prednisolone starting at 60 mg. The upper respiratory tract symptoms were self limiting. Three months later, in the outpatient setting, the patient continued to ambulate independently with further clinical improvement. There was ongoing mild proximal weakness at the hips and mild hypaesthesia to the T10 dermatome. Power was now preserved at the knee, with recovered knee and ankle reflexes.

Discussion

Given the relative paucity of literature regarding SARS-CoV-2 ATM, this case of early ATM represents the neurotropic potential of SARS-CoV-2 and may provide insights for future treatment options [5].

The first report of postinfectious myelitis following SARS-CoV-2 came from Wuhan, China, in March 2020, in a 66-year-old male, 1 week after the onset of fever [6]. Of the 43 cases included in a review of SARS-CoV-2-associated myelitis, 32% had a short-latency period from the onset of symptoms (15 h to 15 days), and 68% had a long-latency period (10 days to 6 weeks) [5]. Cases of short latency may indicate a direct neurotropic effect of the virus, whereas the longer latency periods likely represent postinfectious sequelae [2, 3, 5]. In our case, the time of onset of neurology was approximately 3 days after the onset of respiratory symptoms. Additionally, the CRP was low, which differs from the higher values seen in cases deemed to be caused by postinfective mechanisms [5–7]. Most cases described to date presented with significant respiratory symptoms. Further, given the timing of presentation relative to vaccine administration and the rarity of vaccine-associated demyelination, we deemed it unlikely that this case was vaccine induced [8]. The combination of short-latency, normal inflammatory markers and relative lack of respiratory symptoms makes our case unique compared to previous reports [5]. We surmise that given the lack of a systemic inflammatory response, the findings represent a demyelinating process secondary to direct neurotropic effects of SARS-CoV-2 resulting in ATM.

SARS-CoV-2 enters cells via the human angiotensin-converting enzyme 2 (ACE2) receptor, found to be expressed on a variety of human cells, including glial cells, neurons and on spinal cord neuron membranes [9, 10]. The neurotropism of SARS-CoV-2 is hypothesised to occur via two main mechanisms, either via haematogenous spread or neuronal retrograde dissemination [3]. In the case of haematogenous spread, the blood–brain barrier is compromised following infection of endothelial cells and damage by leukocytes [2, 11]; whereas in retrograde dissemination, the virus enters the olfactory bulb and spreads transneuronally to other parts of the CNS [2, 11].

The detection of SARS-CoV-2 in CSF is rare but has been reported in patients with clinically isolated demyelinating syndrome. [1, 12]. A recent review of 304 COVID-19 patients who underwent lumbar puncture for a neurological syndrome localised to the CNS found only 6% returned a positive SARS-CoV2 PCR on CSF [1, 12]. Explanations for low detection in CSF have been offered, including that the virus is mainly cell bound and spreads cell to cell without invading the CSF or that CSF sampling requires a detection limit that the virus does not reach [1]. Therefore, testing for SARS-CoV-2 in CSF is not well validated and a negative test, in this case, does not rule out neurotropism. In this case, we suggest that evidence of previous CSF positivity combined with our current clinical scenario of short latency supports a case for SARS-CoV-2 neurotropism.

In general, ATM secondary to direct CNS infection is rare, and there is no high-quality evidence to guide treatment. However, both glucocorticoid and antiviral agents are often used in practice. Adopting this principle, this is the first case of SARS-CoV-2 ATM that includes remdesivir in the treatment regimen alongside methylprednisolone. At the time, remdesivir was the only antiviral available for the treatment of SARS-CoV-2 pneumonitis in Australia. As the patient showed no respiratory symptoms, off-label approval was sought. The majority of SARS-CoV-2 myelitis currently described in the literature was treated with high-dose steroids with or without IVIg [5]. The success of these treatments, particularly in the short-latency cases, remains unclear, with only a few cases demonstrating modest improvements within an unclear time frame. [5] Instead, remdesivir is well established in treating COVID-19, and there is evidence for its use in preventing deterioration in early illness [13]. Given this and the limited efficacy data for steroids in short-latency cases, we postulate remdesivir may have potential therapeutic benefit. Our case demonstrated marked improvement with the combination regimen. However, little
is known of the CNS penetration of remdesivir in humans, although animal models have shown limited penetration [14]. Further investigation is required to understand the potential therapeutic effects of remdesivir in early SARS-CoV-2 ATM.

**Conclusion**

ATM is a rare side effect of SARS-CoV-2 infection. In most instances, its occurrence is deemed a result of immune-mediated mechanisms occurring later in the disease course. In this case, we present a patient with ATM presenting on day 3 of illness with little evidence of systemic inflammation. We believe this to be a case of ATM secondary to neurotropism. While more research is required to attain a greater understanding of early SARS-CoV-2 ATM and treatment options, we have observed an impressive clinical response using corticosteroids and remdesivir.

**Conflict of interest**

The authors declare no conflict of interest.

**Author contributions**

Irene F. Lu: Writing – original draft; Writing – review and editing (Lead). Jack S. Cornish: Writing – original draft; Writing – review and editing. Aadith Ashok: Writing – original draft; Writing – review and editing. Siew Kar Chen: Supervision; Writing – review and editing. Eugene Athan: Supervision; Writing – review and editing. Andrew Hughes: Conceptualization; Supervision; Writing – review and editing.

**Ethics statement**

Informed written consent for publication was obtained from the patient included in this study.

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