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

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Abstract. Lu IF, Cornish JS, Ashok A, Chen SK, Athan E, Hughes A. Early SARS-CoV-2-associated acute transverse myelitis: A case for neurotropism? *J Intern Med.* 2022;**00**:1–5.

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 hypercholesterolaemia 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 experienced 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 Glasgow Coma Score of 15, pulse oximetry above 95% on room air and temperature 36°C and was haemodynamically 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 dermatomes 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 weakness had progressed to a 3/5 MRC score at the hip and knee and 4/5 at the ankle bilaterally. Ankle reflexes were now reduced bilaterally with an equivocal Babinski reflex. There was hypoaesthesia towards noxious stimuli, more pronounced 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 unremarkable 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) protein measured mildly high 0.54 g/L, and leucocyte cell count was 8×10^6/L. No organisms were seen on gram stain, and cultures remained negative. CSF PCR testing for Herpesviridae, enterovirus,

Table 1. *Laboratory findings*

Full blood count	Result	Reference range
Haemoglobin (g/L)	140	115–165
Leucocyte count ($\times 10^9$/L)	7.2	4.0–11.0
Neutrophil count ($\times 10^9$/L)	4.7	2.0–8.0
Lymphocyte count ($\times 10^9$/L)	2.1	1.0–4.0
Platelet count ($\times 10^9$/L)	218	150–450
Biochemistry		
CRP (mg/L)	<2.9	<3.0
CK (U/L)	101	<161
TSH (mIU/L)	2.78	0.40–4.00
Vitamin B12 (pmol/L)	614	>180
Folate (nmol/L)	38.6	>10.0
Creatinine (umol/L)	72	45–90
eGFR (ml/min/1.73 m^2)	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

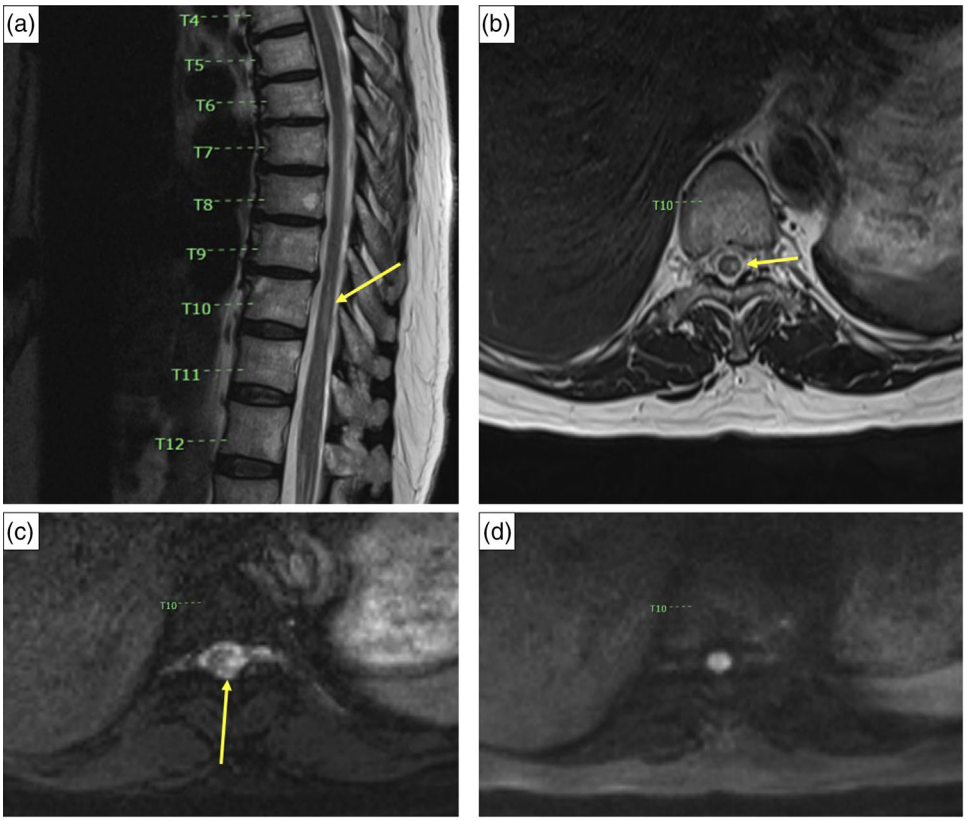

Fig. 1 *Thoracic spine magnetic resonance imaging: (a) Sagittal section, T2 sequencing, identifying a longitudinal focus of signal hyperintensity at the level of T10. (b) Axial section, T2 sequence, small region of hyperintensity noted on the left side of the cord. (c) Diffusion weighted imaging, region of diffusion restriction without corresponding low signal on apparent diffusion coefficient trace (d).*

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 hypoaesthesia 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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