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CASE REPORT

Covid-19 post-infectious acute transverse myelitis responsive to corticosteroid therapy: report of two clinical cases

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Abstract
SARS-COV-2 infection has affected millions of individuals with a wide range of clinical manifestations, including central and peripheral nervous systems through several mechanisms. A rare but potentially severe manifestation of this virus is transverse myelitis. Herein, we report on two patients who developed paraparesis, sensory deficit, and autonomic changes on the tenth day after infection by COVID-19. A 27-year-old man, previously healthy, had symptoms of COVID-19 confirmed by oropharyngeal and nasopharyngeal swab tests. On the tenth day of symptoms, the patient started to experience acute paraparesis, urinary retention, constipation, and hypoesthesia up to the T4 level. The second patient is a 50-year-old man, previously healthy, who had symptoms of the flu-like syndrome. The diagnosis of COVID-19 infection was confirmed by oropharyngeal and nasopharyngeal swab tests. On the tenth day of symptoms, the patient started to experience paraparesis, urinary incontinence, and hypoesthesia up to the T6 level. The neuroimaging and cerebrospinal fluid (CSF) analysis of both patients confirmed acute transverse myelitis after COVID-19 infection. High-dose corticosteroid therapy was started, and both patients showed rapid recovery from their deficits. Although rare, post-infectious transverse myelitis may be related to SARS-COV-2 infection and should be quickly recognized. Although controlled studies are needed, treatment with corticosteroid therapy in high doses was effective in these patients.

Keywords Acute transverse myelitis · Severe acute respiratory syndrome by coronavirus 2 (SARS-COV-2) · Coronavirus · COVID-19

Introduction

SARS-COV-2 infection has affected millions of individuals to date (Zhou et al. 2020). This disease has variable manifestations from an asymptomatic condition up to a rapidly evolving severe pneumonia (Hu et al. 2021). Moreover, this infection may lead to multisystemic involvement, including the central and peripheral nervous systems (Rahman et al. 2020; Whittaker et al. 2020; Moriguchi et al. 2020; Toscano eat al. 2020; Beyrouti et al. 2020; Paterson et al. 2020). One of the neurological manifestations that require prompt recognition is acute transverse myelitis (Chow et al. 2020).

We report below two patients with a recent SARS-COV-2 infection who developed an acute myelitis, with an excellent response to high-dose corticosteroid therapy.

Case 1

A 27-year-old male patient, previously healthy, reported odynophagia, myalgias, fatigue, and subjective fevers. Ten days after the initial symptoms, he described weakness, paresthesias, and hypoesthesia in the lower limbs, and progressive difficulty in urinating and defecating. In the subsequent eight days, he experienced a progressive weakness, impairing his ability to walk.

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Upon hospital admission, on the eighteenth day of symptoms, neurological examination revealed paraparesis with grade 1/5 in the lower limbs. All sensory modalities were affected below the T4 level. The osteotendinous reflexes of the lower limbs were increased and hypoactive in the upper limbs. Bilateral patellar clonus was noted. Cutaneous plantar reflex demonstrated extension bilaterally, and cutaneous abdominal reflexes were absent. The remaining neurological examination was normal.

Preliminary laboratory tests showed lymphopenia (976 cells/μL) and increased C-reactive protein (CRP) (0.46 mg/dL). The analysis of the cerebrospinal fluid (CSF) showed 12 white blood cells (90% lymphocytes), protein 40 mg/dL, glucose 72 mg/dL, and negative CSF polymerase chain reaction (PCR) for COVID-19 (Table 1). Serology cytomegalovirus, HIV, and hepatitis B and C were negative. PCR for herpes virus 1 and 2 was negative in the CSF. SARS-CoV-2 PCR nasopharyngeal swab tested positive on the second day and negative on the tenth day. There were also no clinical or laboratory abnormalities to suggest systemic lupus erythematosus.

Cervical and thoracic spine magnetic resonance imaging (MRI) disclosed multiple foci of non-contiguous hyperintense signals at C6-C7, C7-T1, T2-T4, T6, and T12-L1 levels with damage to the lateral funiculus, anterior spinal horn, and posterior cord, without contrast enhancement (Fig. 1). Brain MRI disclosed no abnormalities. The anti-aquaporin 4 IgG antibody test was negative. Antibodies for anti-myelin-associated glycoprotein IgM were not performed due to local unavailability.

Therapy with intravenous methylprednisolone at a dose of 1 g per day for 5 days improved the symptoms after the third day. On the fifth day after starting treatment, the patient was able to walk with difficulty but without assistance. Continuous motor rehabilitation was carried out. On the 50th day after treatment, the patient had complete recovery of the leg's motor strength, walked without difficulty, and only had mild paresthesias in the feet.

Table 1 Results of laboratory tests of patients 1 and 2

Variables	Patient 1	Patient 2	Reference values
Serum tests			
Hemoglobin (g/dL)	16.4	10.8	13–17.5
Leukocytes (cells/mm^3)	6870	3500	4000–11,000
Lymphocytes (cells/mm^3)	976	893	1000–3500
Platelets (number/mm^3)	307.000	244.000	150,000–450,000
C-reactive protein (mg/dL)	0.46	0.40	< 0.3
PT/INR	1	1	0.8–1.2
aPTT/ratio	1.03	0.92	< 1.25
D-Dimer (ng/ml)	289	1495 l	< 600
Sodium (mM/L)	136	139	136–146
Potassium (mM/L)	3.9	3.9	3.5–5.1
Calcium ionized (mM/L)	1.33	1.25	1.16–1.32
Magnesium (mg/dL)	2.3	1.9	1.6–2.6
Blood Urea Nitrogen (mg/dL)	37	17	15–50
Creatinine (mg/dL)	0.83	0.6	0.5–1.3
RT- PCR for SARS-CoV-2 (naso/oropharynx)	D2 symptoms: positive D10 symptoms: negative	D5 symptoms: positive D15 symptoms: negative	Negative Negative
Analysis of cerebrospinal fluid			
Cells (cells/mm^3)	12	4	0–4
Cells differential	90% lymphocytes	100% lymphocytes	-
Protein (mg/dL)	40	46.6	15–45
Glucose (mg/dL)	72	74	-
VDRL	Not reactive	Not reactive	Not reactive
Bacteria research (Gram stain)	Negative	Negative	Negative
Fungal research	Negative	Negative	Negative
PCR Herpes simplex vírus type 1 and 2	Not detected	Not detected	Not detected
Cytomegalovirus IgG and IgM	Not detected	Not detected	Not detected
RT-PCR for SARS-CoV-2	Not detected	Not tested	Not detected

PT prothrombin time, *aPTT* activated partial thromboplastin time, *VDRL* Venereal Disease Research Laboratory, *PCR* polymerase chain reaction

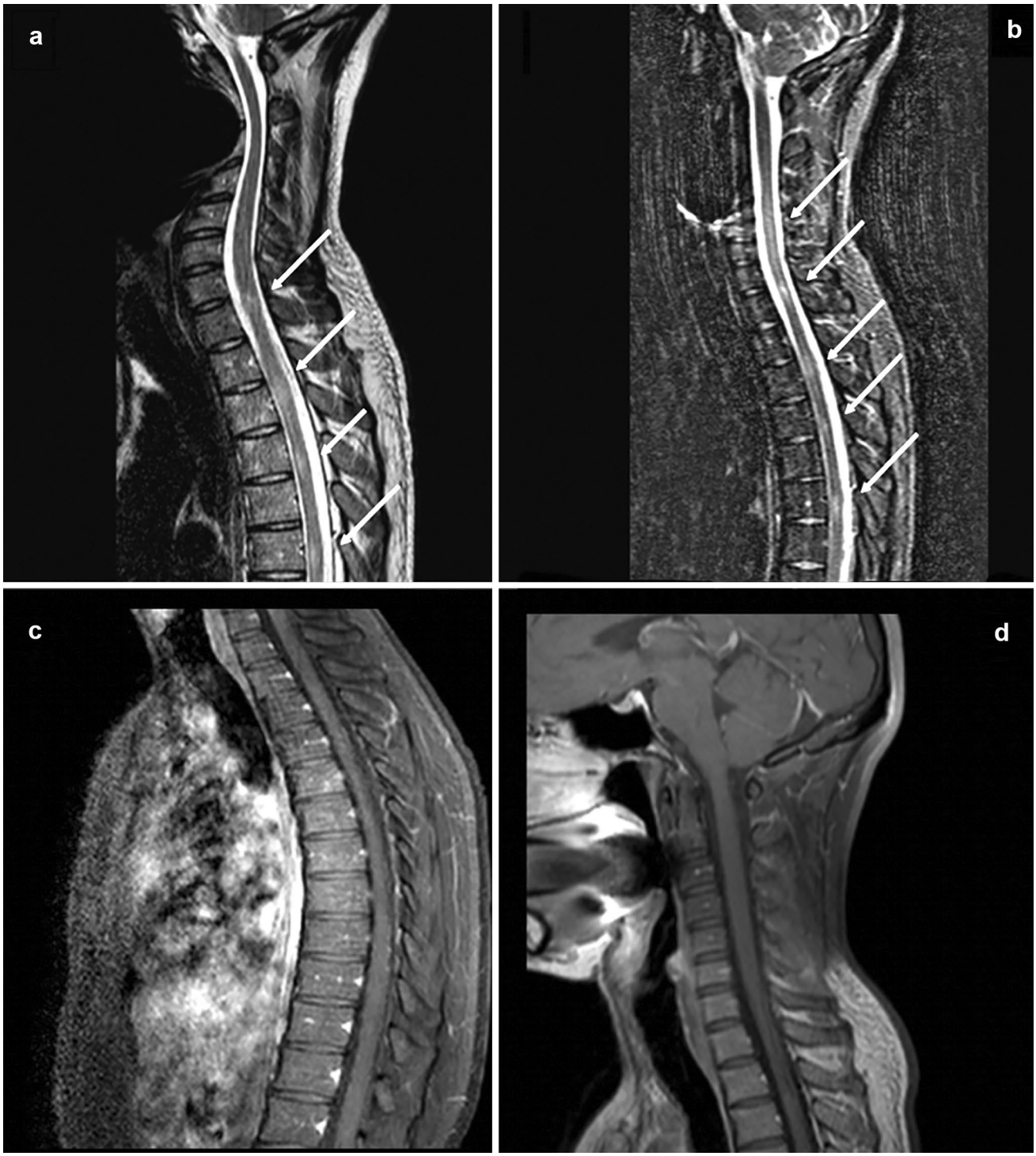

Fig. 1 MRI of the cervical and thoracic spine of patient 1 demonstrating multiple foci of hyperintense signal on T2-weighted sequences, non-contiguous at C6-C7, C7-T1, T2-T4, T6, and T12-L1 with damage to the lateral funiculus, anterior spinal horn, and posterior cord (arrows). **a** Sagittal T2-weighted image of cervical and thoracic spine. **b** Sagittal T2-weighted image of cervical and thoracic spine. **c** Sagittal T1-weighted image of thoracic spine after the administration of gadolinium contrast. **d** Sagittal T1-weighted image of cervical spine after the administration of gadolinium contrast

Case 2

A 50-year-old male patient, previously healthy, described odynophagia, anosmia, dysgeusia, fever, and rhinorrhea. SARS-CoV-2 PCR nasopharyngeal swab tested positive on the fifth day of symptoms. The patient reported progressive reduction in strength of the lower limbs, more pronounced on the left, associated with decreased sensitivity in the lower limbs, urinary urgency and incontinence, and constipation. On the seventeenth day of illness, he went to the emergency room with difficulty walking.

On admission, he was afebrile, eupneic, with $SatO_2$ 99%. Neurological examination revealed paraparesis with grade 3/5 in the lower limbs, and a sensory level at T6. The osteotendinous reflexes of the lower limbs were enhanced and normoactive in the upper extremities with bilateral extensor cutaneous plantar reflexes and absent cutaneous abdominal reflexes. The remaining neurological examination was normal.

Preliminary laboratory tests showed anemia (10.8 g/dL), lymphopenia (893/µL), and CRP elevation (4.40 mg/dL). CSF analysis showed 4 white blood cells (100% lymphocytes), protein 46.6 mg/dL, and glucose 74 mg/dL (Table 1). Serologies for cytomegalovirus, HIV, and hepatitis B and C were negative. PCR for herpes virus 1 and 2 was negative in the CSF.

The cervical and thoracic spine MRI revealed a hyperintense signal on T2-weighted sequences at the T5-T6 level in the anterolateral spine, predominantly on the left, and enhancing lesions at C2, C7-T1, and T11 (Fig. 2). The patient required early discharge, and brain MRI could not be performed in time. Anti-aquaporin 4 IgG and anti-myelin-associated glycoprotein IgM were not available for analysis. There were no other clinical or laboratory findings suggesting autoimmune systemic disease.

After the treatment with intravenous methylprednisolone, 1 g per day for 5 days, the patient demonstrated a favorable response, with the progressive recovery of strength, and he was able to walk without assistance. After 30 days following hospital discharge, the patient had normal strength throughout all limbs, with enhanced osteotendinous, extensor cutaneous plantar reflexes, and mild hypoesthesia in the feet.

Discussion

In this article, we described two cases of patients who developed acute transverse myelitis following SARS-CoV-2 infection. Both patients, unlike those previously reported, had a good and rapid response to high doses of methylprednisolone. Transverse myelitis is defined as an inflammation in the spinal cord with acute and subacute inflammation, and may be secondary to autoimmunity, occurring in the post- or para-infectious period (Beh et al. 2013).

The post-infectious etiology related to the immune attack by molecule mimicry has been well established with pathogens such as Mycoplasma pneumoniae and may be the mechanism involved in the spinal cord injury related to SARS-COV-2 (Tsiodras et al. 2006). The negative results of viral PCR in samples from nasopharynx and oropharynx in the presence of neurological manifestations, negative results for SARS-COV-2 in the cerebrospinal fluid (CSF) analysis in case 1, and the response to corticosteroid therapy reinforce these hypotheses.

Another possible causal mechanism is the direct viral invasion of the central nervous system. Among these mechanisms, angiotensin-converting enzyme 2 (ACE-2) expression seems to play an essential role through the infection of the olfactory epithelium and retrograde transsynaptic viral infection. Moreover, the breakdown of the blood–brain barrier with infection of vascular endothelial cells and T lymphocytes could also explain this invasion (Zubair et al. 2020).

Zhao et al. (2020) were the first to describe a patient with myelitis related to COVID-19. They reported on a 66-year-old man who presented with paraparesis and urinary retention 5 days after the onset of the symptoms. The patient used dexamethasone 10 mg for 10 days, followed by immunoglobulin, demonstrating slight improvement, and then was referred for neurological rehabilitation (Zhao et al. 2020).

Valiuddin et al. (2020) reported a 61-year-old patient with a transverse myelitis 7 days after SARS-COV-2 infection. The patient was treated with methylprednisolone with no clinical improvement, requiring plasmapheresis and achieving a partial response. Then, Shahali et al. (2021) reported a 63-year-old man who developed myelitis after 4 days of COVID-19-related symptoms, which worsened after using methylprednisolone and improved after immunoglobulin (Valiuddin et al. 2020; Shahali et al. 2021).

Unlike these previous reports, the two patients in our study showed a good response to corticosteroid therapy. The differences in the doses and the treatment time may explain these different responses. In our cases reported, we prescribed methylprednisolone 1 g/day for 5 days with treatment started relatively early, 10 days after the onset of neurological symptoms in the first case, and 9 days in the second case. In the case described by Zhao et al. (2020), dexamethasone was prescribed at a lower corresponding methylprednisolone dose than that used to treat these two patients (Zhao et al. 2020). Shahali et al. (2021) administered 3 days of methylprednisolone, and these two patients were treated for five days (Shahali et al. 2021). It is not clear from these other case reports the time between the

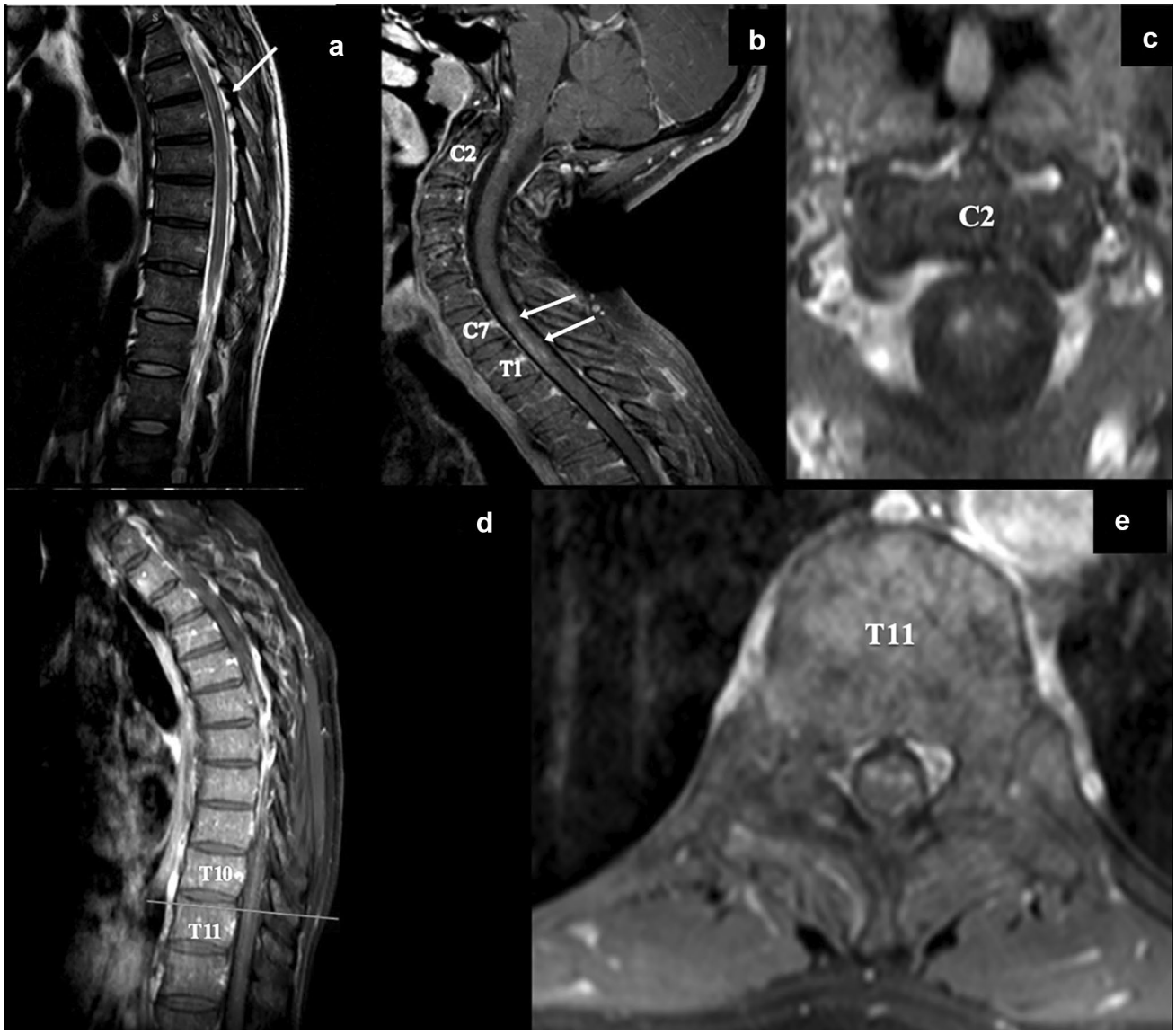

Fig. 2 MRI of the cervical and thoracic spine of patient 2 demonstrating a hyperintense signal on T2-weighted sequences at T5–T6, affecting the anterolateral spine, predominantly on the left, and enhancing lesions at C2, C7-T1, and T11 (arrows). **a** Sagittal T2-weighted image of thoracic spine. **b** Sagittal T1-weighted image of cervical spine after the administration of gadolinium contrast. **c** Axial T1-weighted image at C2 after the administration of gadolinium contrast. **d** Sagittal T1-weighted image of thoracic spine after the administration of gadolinium contrast. **e** Axial T1-weighted image at T11 after the administration of gadolinium contrast

onset of neurological symptoms and the prescription of corticosteroid therapy. The patients described in this report are younger than other cases reported and had no comorbidities. Furthermore, the different variants of the virus circulating could induce different immune responses.

The differential diagnosis of acute inflammatory transverse myelitis (ATM) is broad. Clinical, laboratory, and radiological findings of non-compressive myelopathies can be used to distinguish between infectious, inflammatory, demyelinating, vascular, neoplastic, and paraneoplastic etiologies. It was not possible to completely exclude other etiologies due to unavailability of resources and the need for early discharge. Although rare, post-infectious transverse myelitis can be seen with SARS-COV-2 infection and should be quickly recognized. Although controlled studies are needed, treatment with corticosteroid therapy in high doses was effective in these patients.

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Declarations

Ethics statement Patients signed an informed consent and allowed publication of this data.

Conflict of interest The authors declare no competing interests.

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