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Pearls & Oy-sters: Hemorrhagic Myelitis Following SARS-CoV-2 Infection

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Abstract

Hemorrhage in the setting of myelitis is rarely seen in clinical practice. We report a series of 3 women aged 26, 43, and 44 years, who presented with acute hemorrhagic myelitis within 4 weeks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Two required intensive care, and 1 had severe disease with multiorgan failure. Serial MRI of the spine demonstrated T2-weighted hyperintensity with T1-weighted postcontrast enhancement in the medulla and cervical spine (patient 1) and thoracic spine (patients 2 and 3). Hemorrhage was identified on precontrast T1-weighted, susceptibility-weighted, and gradient echo sequences. Distinct from typical inflammatory or demyelinating myelitis, clinical recovery was poor in all cases, with residual quadriplegia or paraplegia, despite immunosuppression. These cases highlight that although hemorrhagic myelitis is rare, it can occur as a post/parainfectious complication of SARS-CoV-2 infection.

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Pearls

- Hemorrhagic myelitis can occur in the setting of acute or subacute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
- In case of suspected myelitis in the setting of SARS-CoV-2 infection, investigations should include gradient echo sequences with MRI of the spinal cord to detect potential hemorrhage.

Oy-sters

- Hemorrhagic myelitis in the setting of SARS-CoV-2 infection does not seem to be correlated with the severity of systemic symptoms due to initial viral infection.
- Para/postinfectious hemorrhagic myelitis responds poorly to immunosuppressive therapies and can result in severe disability.

Case Series

Case 1

A 43-year-old woman presented with acute bilateral lower extremity weakness, urinary retention, and ascending sensory loss 10 days after developing upper respiratory tract infection symptoms. A nasopharyngeal swab showed positive results on SARS-CoV-2 PCR testing. Neurologic examination was notable for flaccid paraplegia and T4 sensory level. Spine MRI at 24 hours showed contrast enhancement and central T2-weighted hyperintensity with expansion from C5-T12 (Figure 1A). Aortogram was normal. Same day, the CSF demonstrated 226 erythrocytes/μL (normal <5/μL), pleocytosis (949 leukocytes/μL, normal <5/μL, 93% neutrophils), elevated protein (210 mg/dL, normal 15–45 mg/dL), and elevated immunoglobulin (Ig) G index (0.82, normal <0.61). CSF infectious studies, including meningoencephalitis panel (Biofire Filmarray), herpes simplex virus (HSV) PCR, varicella zoster virus (VZV) serology, SARS-CoV-2 PCR, and autoimmune myelopathy neural antibody panel (Mayo Clinic laboratories), showed negative results. HIV serology, antinuclear antibodies (ANAs), aquaporin (AQP)–4 IgG, and myelin

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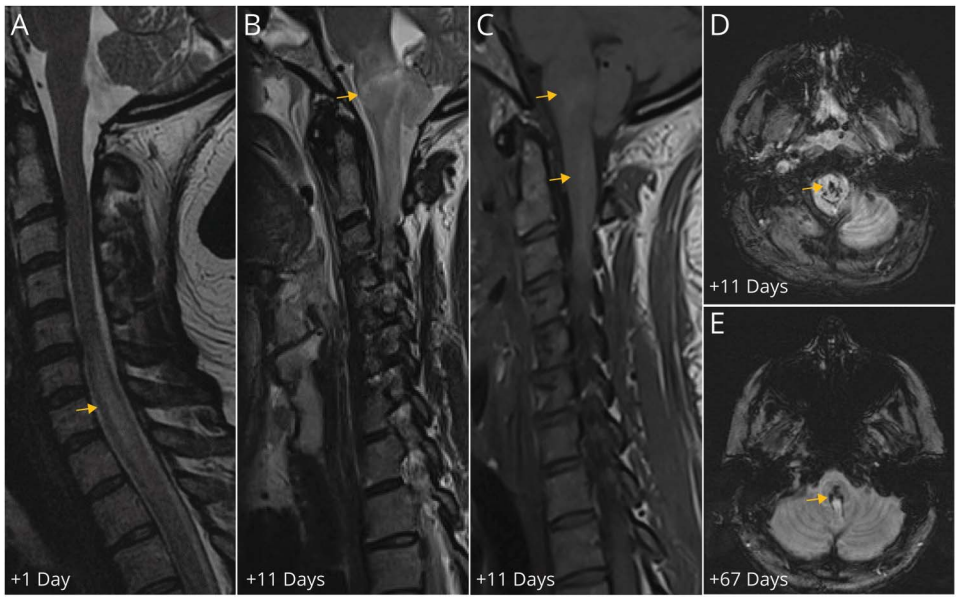
Figure 1 Progression of MRI Changes for Case 1



Panel A demonstrates a sagittal T2-weighted image with diffuse central cord signal abnormality extending superiorly from C5-6 through T11-T12 (thoracic component and corresponding T1-weighted contrast-enhancing sequence not included in this image) at 24 hours. Panel B shows significant progression of signal abnormality superiorly into brainstem on sagittal T2-weighted image with associated precontrast T1-weighted hyperintensity from suspected methemoglobin (panel C) and corresponding susceptibility-weighted imaging (SWI) hypointensity at 11 days (panel D). Panel E shows persistence of blood byproducts on SWI (hemosiderin, shown by arrow) at 67 days.

oligodendrocyte glycoprotein (MOG) IgG antibodies by cell-based assay (CBA) showed negative results. Platelets, prothrombin time (PT), and activated partial thromboplastin time (APTT) were normal. Prophylactic subcutaneous enoxaparin (40 mg daily) was administered.

She received 1 g of IV methylprednisolone (IVMP) for 5 days (11 days after neurologic symptom) but progressed to quadriplegia and respiratory failure, so plasmapheresis was initiated. Repeat spine and brain MRI (11 days after neurologic symptom) showed extension of T2-weighted hyperintensity superiorly into the brainstem with new hemorrhage demonstrated as precontrast T1-weighted hyperintensity (Figure 1, B and C) and susceptibility-weighted imaging (SWI) hypointensity (Figure 1D). Repeat CSF analysis (12 days after neurologic symptom) showed 5 erythrocytes/μL, 5 leukocytes/μL (51% lymphocytes), 31 mg/dL of protein, and elevated IgG index (1.09). IV immunoglobulin (IVIG) was administered (2 mg/kg total dose over 5 days), and another 5-day course of 1 g of IVMP was administered, followed by oral prednisone taper (60 mg daily, tapered by 5 mg weekly).

She remained quadriplegic and mechanically ventilated. Repeat neuroimaging at 2 months showed improvement in lower cervical T2-weighted hyperintensity and evolving SWI hypointensity in the medulla (Figure 1E). At 3 months, the expanded disability status scale (EDSS) was 9.0, and modified Rankin score (mRS) was 5.

Case 2

A 44-year-old woman with a history of unilateral episcleritis and right lower extremity paresthesia and weakness presented with new symmetrically ascending paresthesia in bilateral lower extremities, 3 weeks after symptomatic SARS-CoV-2 infection with anosmia, ageusia, and upper respiratory tract infection symptoms.

Initial neurologic examination demonstrated intact power, hyperreflexia, and sensory level to T8. Spine MRI (1 month after neurologic symptom) showed expansile T2-weighted hyperintensities at T6-8 and T9-10 (Figure 2A) with contrast enhancement. Brain MRI showed multiple periventricular and pericallosal nonenhancing T2-weighted lesions. Same day CSF analysis showed 94 erythrocytes/μL, 7 leukocytes/μL (94% lymphocytes), 32 mg/dL of protein, elevated IgG index (1.77), and serum-unmatched oligoclonal bands in the CSF. CSF bacterial stain and culture and viral studies (cytomegalovirus [CMV], VZV, and HSV) showed negative results. Serum HIV, ANA, AQP-4 IgG, and MOG IgG antibodies by CBA showed negative results. Platelets, PT, and APTT were normal. She received 1 g of IVMP daily for 3 days. Two weeks later, she developed paraplegia and urinary retention. Repeat imaging (9 weeks after symptom onset) showed near-confluent progression of T2-weighted hyperintensity from C2-L1 (Figure 2B) with patchy contrast enhancement. She received a 5-day course of 1 g of IVMP and plasmapheresis, and an oral prednisone taper was started (60 mg daily, tapered by 10 mg weekly). She received rituximab-pvvr.

Repeat imaging at 4 months showed improvement in T2-weighted hyperintensity and evolution to chronic hemorrhage at T6-T7 on precontrast T1-weighted imaging (Figure 2C) and axial gradient echo. At approximately 8 months, she remained paraplegic (mRS = 5, EDSS = 8.0), with resolving precontrast T1-weighted hyperintensity and

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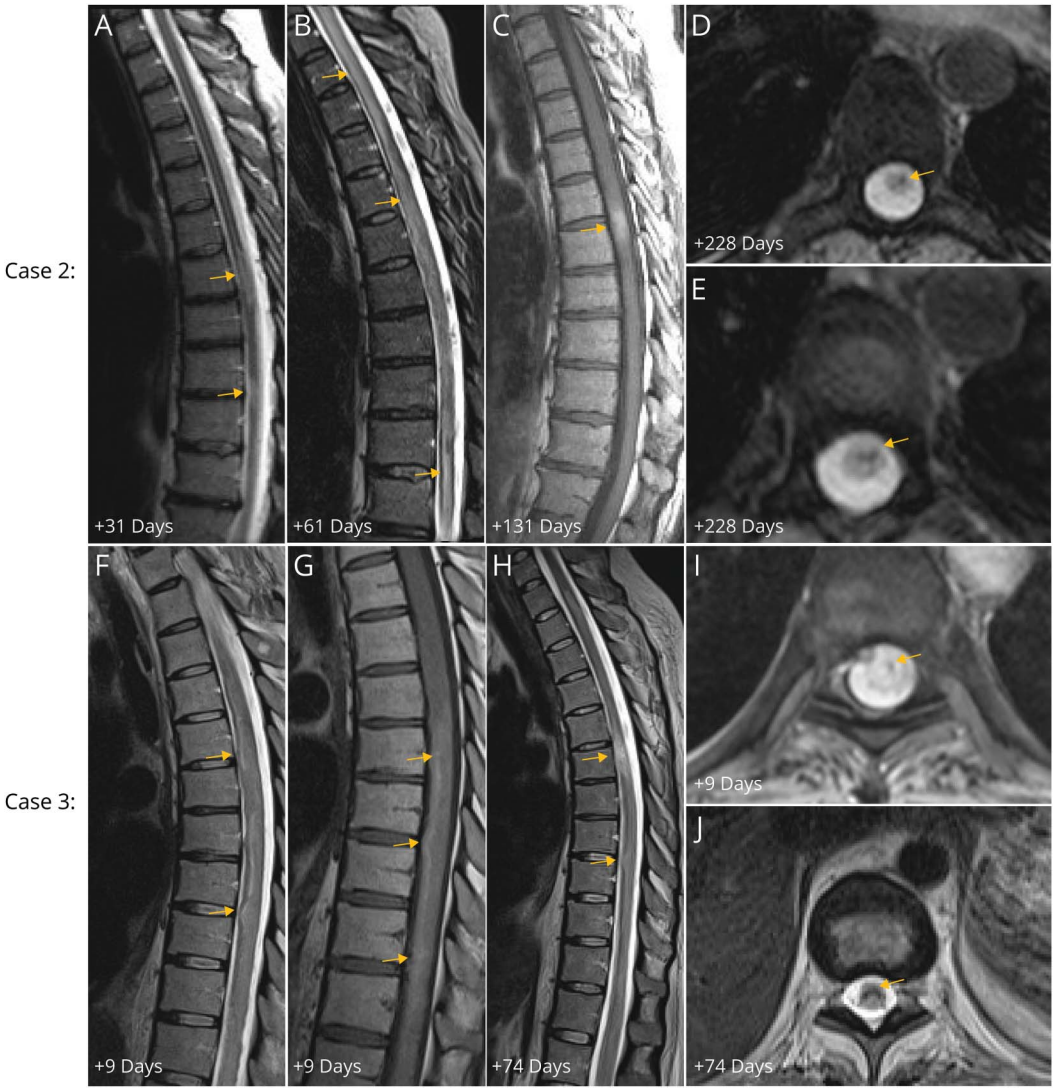
Figure 2 Progression of MRI Changes for Case 2 (A–E) and Case 3 (F–J)



Panel A demonstrates a sagittal T2-weighted image showing mild expansile hyperintensity within the central cord at T6-T8 and T9-T10 (corresponding contrast enhancement on T1-weighted imaging not shown) at 31 days, with subsequent progression to confluent expansion and central T2-weighted hyperintensity extending from C2 to L1 at 61 days (panel B). Panel C demonstrates precontrast T1-weighted hyperintensity corresponding to areas of hemorrhage, also seen on panels D and E, which show chronic blood byproducts on axial T2-weighted 2-dimensional fast low-angle shot sequence at 228 days. Panel F demonstrates a sagittal T2-weighted image at 9 days notable for extensive expansile cord signal abnormality through the entire cord (T1 to conus) along with precontrast T1-weighted hyperintensity in panel G. Microhemorrhage is demonstrated on axial T2-weighted 2-dimensional multiecho sequence at 9 days in panel I. Panel H demonstrates multifocal T2-weighted hyperintensity and expansile central cord abnormalities throughout the cord with more conspicuous appearance of blood byproducts on turbo spin-echo sequence on panel J.

blood byproducts on T2-weighted 2-dimensional fast low-angle shot sequence (Figure 2, D and E). Spine MRI at 1 year showed myelomalacia (T5-T9).

Case 3

A 26-year-old woman was admitted for COVID-19 myocarditis, cardiogenic shock, and multiorgan failure. Ten days of dexamethasone was given as part of symptomatic infection treatment. She was vaccinated with the adenovirus-vectored COVID-19 vaccine (Janssen Biotech) 5 months before symptomatic infection. Four weeks into her illness, she developed acute ascending sensory loss, followed by flaccid paraplegia and areflexia, reaching nadir over 1 week. The CSF (3 days after neurologic symptom) demonstrated 23 erythrocytes/μL, 3 leukocytes/μL (75% neutrophiles), 36 mg/dL of protein, and matched oligoclonal bands. Thoracic spine MRI (9 days after neurologic symptom) showed expansile T2-weighted hyperintensity (T1 to conus) with precontrast T1 hyperintensity and microhemorrhage on T2-weighted 2-dimensional multiecho sequences (Figure 2, F, G, and I). Aortogram was normal. Repeat CSF analysis (19 days after previous) showed 2 erythrocytes/μL, 1 leukocyte/μL (55% lymphocytes), 36 mg/dL of protein, and slightly elevated IgG index (0.67). Infectious studies including CSF HSV (PCR), VZV, CMV, and Epstein-Barr virus serologies showed negative results. Serum HIV, ANA, and CSF autoimmune

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encephalopathy autoantibody panels showed negative results (Mayo Clinic laboratories). Platelets, PT, and APTT were normal. Prophylactic subcutaneous heparin (5,000 units twice daily) had been administered. Serum AQP-4 IgG and MOG IgG antibodies by CBA showed negative results. She received 5 doses of 1 g IVMP (13 days after neurologic symptom), followed by oral prednisone taper (40 mg daily, tapered by 10 mg weekly). Repeat imaging at 2 months showed persistent T2-weighted hyperintensity and hemorrhage on turbo spin-echo sequences (Figure 2, H and J). At 5 months, she remained paraplegic (mRS = 5, EDSS = 8.0).

Discussion

Spinal cord hemorrhage in the setting of myelitis is rare and has been predominantly reported in postinfectious settings. In this study, we describe 3 women with post–SARS-CoV-2 myelitis with hemorrhagic transformation. Symptom severity from SARS-CoV-2 infection ranged from mild to severe, and the latency to neurologic symptoms was subacute. Spine MRI showed intrinsic T1 hyperintensity and hemorrhage on gradient echo sequences in all patients. All patients received immunosuppression but had minimal response with severe disability (EDSS 8–9) at the last follow-up.

Five other cases of hemorrhagic myelitis post–SARS-CoV-2 infection were reported.[1-5] The average onset of neurologic deficits was 11 days (range 3–21 days) after initial infection symptoms, the temporality favoring a para/postinfectious pathogenesis.[6] Similar to our cases, myelitides were predominantly longitudinally extensive on MRI. The CSF most commonly showed lymphocytic pleocytosis. Treatment included steroids and plasmapheresis (4 patients), supportive care (1 patient), and rituximab (1 patient).[1-5] After steroids and plasmapheresis, 1 patient subsequently received cyclophosphamide, IVIG, and eculizumab.[5] Despite immunosuppression, minimal or no improvement was noted during follow-up (8 days–9 months), with severe neurologic outcomes.[1-5]

There are sparse reports of para/postinfectious hemorrhagic myelitis dating back to 1915 with histopathology demonstrating hemorrhagic changes involving the gray matter with early necrotizing features and perivascular lymphocytic infiltration.[7] Other para/postinfectious hemorrhagic myelitis cases reported include herpes viruses (HSV-1 and HSV-2,[8] VZV,[9,10] and CMV[10]) and immunocompromised patients (HIV, leukemia, or pregnancy).[8-10] Few noninfectious cases include those occurring in the setting of vaccination (papilloma[11] and influenza viruses[12]), comorbid systemic lupus erythematosus, and idiopathic cases.[12]

The key clinical features of hemorrhagic myelitis compared with inflammatory or demyelinating myelitis are the severity of the neurologic deficit (flaccid paralysis) with minimal clinical response to immunosuppressive therapies and severe long-term neurologic disability. The key radiologic features of hemorrhagic myelitis are the detection of blood products on gradient echo imaging with hypointensity in the hemorrhagic area. Early hemorrhage on a T1-weighted sequence is initially isointense, progressing to T1-weighted hyperintensity due to paramagnetic dephasing from methemoglobin in early subacute phase. In late subacute phases, T2-weighted hyperintensities are noted, and in the chronic phase, the lesion becomes both T1-weighted and T2-weighted hypointense due to multivoxel susceptibility effects from hemosiderin. Subacute myelopathy due to structural or vascular lesions can be distinguished from hemorrhagic myelitis by insidious onset and longer duration of symptoms with continued progression and interval fluctuations.[13] Early clinical nadir (hours to days) is more suggestive of a spinal cord infarct, whereas it may take days to weeks in case of myelitis.[13]

There are several proposed mechanisms for hemorrhagic myelitis, including tissue necrosis.[5] Others may include direct neuroinvasive viral mechanisms, para/postinfectious cellular inflammatory cascades, and complement activation, vasculopathy, or coagulopathy.[6,14] Cytokine profiling in acute SARS-CoV-2 infection shows interleukin-6 and interleukin-8 production is induced regardless of disease severity, suggesting inflammatory cascade activation may not correlate to systemic or neurologic symptom severity.[15] The temporal evolution on neuroimaging suggests hemorrhage may occur after the initial inflammatory stage of the illness, as necrotic changes are induced and evolve, which reflects neurovascular dysfunction. Similarly, acute hemorrhagic necrotizing leukoencephalitis is a rare severe postinfectious manifestation, which evolves after an initial inflammatory event.

Hemorrhagic myelitis is rarely seen in clinical practice, but may occur in a para/postinfectious setting including post–SARS-CoV-2. In cases of postinfectious myelitis with severe neurologic deficits, it may be prudent to consider imaging to detect hemorrhage including gradient echo sequences.

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