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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 three women aged 26, 43, and 44 years-old, who presented with acute hemorrhagic myelitis within 4 weeks of SARS-CoV-2 infection. Two required intensive care and one had severe disease with multi-organ failure. Serial magnetic resonance imaging (MRI) of the spine demonstrated T2-weighted hyperintensity with T1-weighted post-contrast enhancement in the medulla and cervical spine (patient 1), and thoracic spine (patients 2 and 3). Hemorrhage was identified on pre-contrast 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/para-infectious complication of SARS-CoV-2 infection.

Pearls

- Hemorrhagic myelitis can occur in the setting of acute or subacute 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 imaging of the cord to detect potential hemorrhage.

Oy-sters

- Hemorrhagic myelitis in the setting of SARS-CoV-2 infection does not appear to be correlated with severity of systemic symptoms due to initial viral infection.
- Para/post-infectious 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. Nasopharyngeal swab was positive on SARS-CoV-2 polymerase chain reaction (PCR) testing. Neurological exam was notable for flaccid paraplegia and T4 sensory level. Spine magnetic resonance imaging (MRI) at 24 hours showed contrast-enhancement and central T2-weighted hyperintensity with expansion from C5-T12 (Figure 1A). Aortogram was normal. Same day, cerebrospinal fluid (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 IgG index (0.82, normal <0.61). CSF infectious studies, including meningoencephalitis panel (Biofire Filmarray), herpes simplex virus (HSV) polymerase chain reaction (PCR), varicella zoster virus (VZV) serology, SARS-CoV-2 PCR, and autoimmune myelopathy neural antibody panel (Mayo Clinic laboratories) were negative. Human immunodeficiency virus (HIV) serology, anti-nuclear antibodies (ANA), aquaporin (AQP)-4 IgG and myelin oligodendrocyte glycoprotein (MOG) IgG antibodies by cell-based assay (CBA) were negative. Platelets, prothrombin time (PT) and activated partial thromboplastin time (APTT) were normal. Prophylactic subcutaneous enoxaparin 40 mg daily was administered.

She received 1g of intravenous 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 pre-contrast T1-weighted hyperintensity (Figure 1, B–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). Intravenous immunoglobulin (IVIG) was administered (2 mg/kg total dose over 5 days) and another 5-day course of 1g IVMP, 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, expanded disability status scale (EDSS) was 9.0 and modified Rankin score (mRS) was 5.

Case 2

A 44-year-old woman with 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 (one 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 non-enhancing 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 unmatched oligoclonal bands in the CSF. CSF bacterial stain and culture, and viral studies (cytomegalovirus - CMV, VZV, HSV) were negative. Serum HIV, ANA, AQP-4 IgG and MOG IgG antibodies by CBA were negative. Platelets, PT, and APTT were normal. She received 1g IVMP daily for 3 days, which was started upon imaging interpretation. 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 1g IVMP, completed 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 pre-contrast T1-weighted imaging (Figure 2C) and axial gradient echo. At approximately 8 months she remained paraplegic (mRS=5, EDSS=8.0), with resolving pre-contrast T1-weighted hyperintensity and blood by-products on T2-weighted two-

dimensional fast low angle shot sequence (Figure 2, D–E). Spine MRI at one year showed myelomalacia (T5-T9).

Case 3

A 26-year-old woman was admitted for COVID-19 myocarditis, cardiogenic shock and multi-organ 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) five months before symptomatic infection. Four weeks into her illness she developed acute ascending sensory loss, followed by flaccid paraplegia and areflexia, reaching nadir over one week. 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 pre-contrast T1 hyperintensity and microhemorrhage on T2-weighted two-dimensional multi-echo sequences (Figures 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, slightly elevated IgG index (0.67). Infectious studies including CSF HSV (PCR), VZV, CMV, and Epstein-Barr virus serologies were negative. Serum HIV, ANA, and CSF autoimmune encephalopathy autoantibody panels were negative (Mayo Clinic laboratories). Platelets, PT, and APTT were normal. Prophylactic subcutaneous heparin (5000 units twice daily) had been administered. Serum AQP-4 IgG and MOG IgG antibodies by CBA were negative. She received 5 doses of 1g 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 post-infectious settings. Here, 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 last follow-up.

Five other cases of hemorrhagic myelitis cases post-SARS-CoV-2 infection were reported.[1-5] The average onset of neurologic deficits was 11 days (range 3-21 days) following initial infection symptoms, the temporality favoring a para/post-infectious pathogenesis.[6] Similar to our cases, myelites were predominantly longitudinally extensive on MRI. CSF most commonly showed lymphocytic pleocytosis. Treatment included steroids and plasmapheresis (4 patients), supportive care (1 patient), rituximab (1 patient).[1-5] Following steroids and plasmapheresis, one patient subsequently received cyclophosphamide, IVIG, 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/post-infectious hemorrhagic myelitis dating back to 1915 with histopathology demonstrating hemorrhagic changes involving the grey matter with early necrotizing features and perivascular lymphocytic infiltration.[7] Other para/post-infectious hemorrhagic myelitis cases reported include herpes viruses (HSV-1 and -2[8], VZV[9, 10], CMV[10]) and immunocompromised patients (HIV, leukemia, or pregnancy).[8-10] Few non-infectious 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 to 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 multi-voxel 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 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] Other may include direct neuroinvasive viral mechanisms, para/post-infectious 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, and which reflects neurovascular dysfunction. Similarly, acute hemorrhagic necrotizing leukoencephalitis is a rare, severe post-infectious manifestation which evolves after an initial inflammatory event.

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

References

1. Sotoca J, Rodríguez-Álvarez Y. COVID-19-associated acute necrotizing myelitis. Neurol Neuroimmunol Neuroinflamm. 2020;7: e803.
2. Wong PF, Craik S, Newman P, et al. Lessons of the month 1: A case of rhombencephalitis as a rare complication of acute COVID-19 infection. Clin Med. 2020; 20:293–294.
3. Kaur H, Mason JA, Bajracharya M, et al. Transverse Myelitis in a Child With COVID-19. Pediatric Neurology. 2020; 112:5–6.

4. Maghrabi Y, Baeesa SS. Acute Hemorrhagic Myelitis in an Adolescent With COVID-19: A Case Report and Review of Literature. Cureus 13(12): e20553.
5. Guada L, Rocha Cabrero F, Baldwin NL, Levi AD, Gultekin SH, Verma A. Acute Ascending Necrotizing Myelitis After COVID-19 Infection: A Clinicopathologic Report. Neurol Clin Pract. 2022; 12(3): e28-e32.
6. Schulte EC, Hauer L, Kunz AB, Sellner J. Systematic review of cases of acute myelitis in individuals with COVID- 19. Eur J Neurol. 2021; 28:3230–3244.
7. Burley BT. Acute ascending hemorrhagic myelitis. JAMA. 1915; 65(17):1448-1455.
8. Nakajima H, Shoji H. Chapter 10: Herpes Simplex Myelitis: Differences in Clinical Manifestations Between Herpes Simplex Virus Type 1 and Type 2. In: Hayasaka D, ed. *Pathogenesis of Encephalitis*. Rijeka: InTech; 2011:153-168.
9. Chang CC, McLean C, Vujovic O, Jenney AJ, Short M, Lyon S, Storey E, Lewin SR. Fatal acute varicella-zoster virus hemorrhagic meningomyelitis with necrotizing vasculitis in an HIV-infected patient. Clin Infect Dis. 2009; 48(3):372-3.
10. Pohlen SM, Lin JS, Wang KY, Ghasemi-Rad M, Lincoln CM. Haemorrhagic conversion of infectious myelitis in an immunocompromised patient. BMJ Case Rep. 2017; bcr2017221866.
11. Badarny S, Badarny Y, Goldfeld M, Wakid H. Hemorrhagic Myelitis after Papilloma Virus (HPV) Vaccination. Aust J Mult Scler & Neuroimmunol. 2020; 5(1):1032-4.
12. Howard CW, Racosta JM, Robinson DB. Acute hemorrhagic longitudinally extensive transverse myelitis –A case report and review of the literature. Neuroimmunology Reports. 2022; 2:100051.
13. Schmalstieg WF, Weinshenker BG. Approach to acute or subacute myelopathy. Neurology. 2010;75(18 Suppl 1):S2-8
14. Lee MH, Perl DP, Steiner J, Pasternack N, Li W, Maric D, Safavi F, Horkayne-Szakaly I, Jones R, Stram MN, Moncur JT, Hefti M, Folkerth RD, Nath A. Neurovascular injury with complement activation and inflammation in COVID-19. Brain. 2022; 145(7):2555-2568.

15. Guasp M, Muñoz-Sánchez G, Martínez-Hernández E, Santana D, Carbayo Á, Narnjo L, Bolós U, Framil M, Saiz A, Balasa M, Ruiz-García R, Sánchez-Valle R, The Barcelona Neuro-COVID-Study Group. CSF Biomarkers in COVID-19 Associated Encephalopathy and Encephalitis Predict Long-Term Outcome. Front Immunol. 2022; 13:866153.

Figure titles and legends

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 pre-contrast 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.

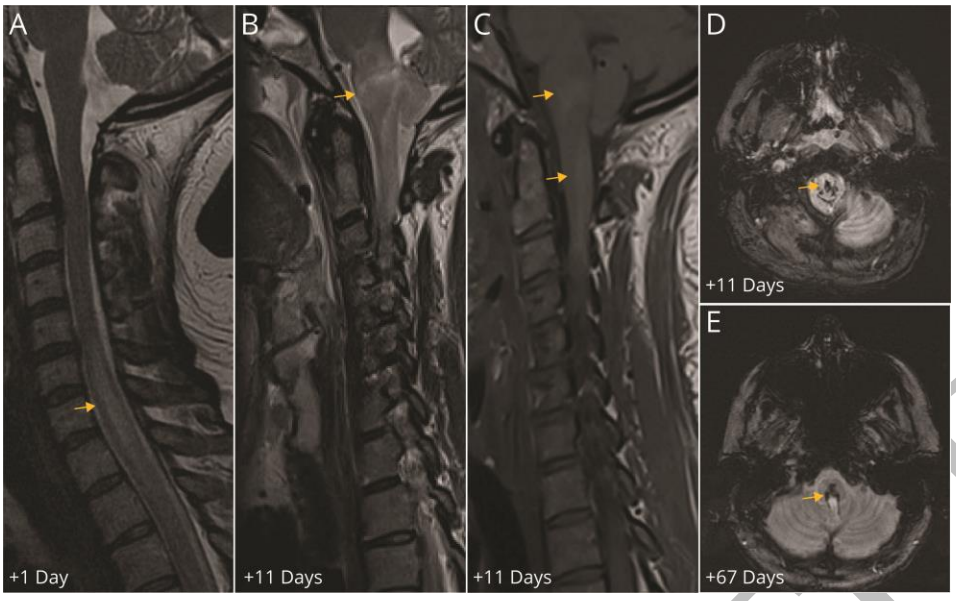
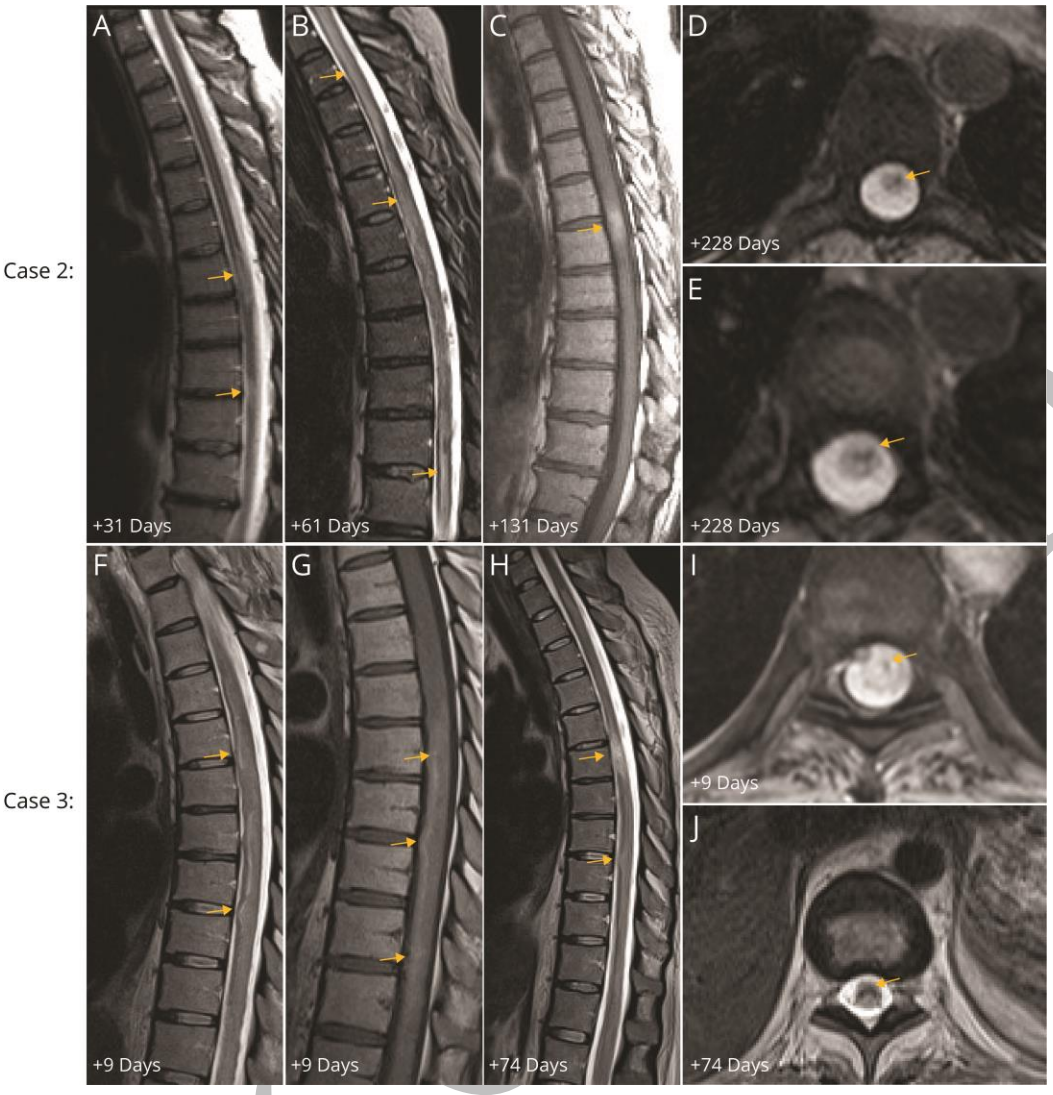


Figure 2. Progression of MRI changes for Case 2 (A-E) and Case 3(F-J).

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 pre-contrast T1-weighted hyperintensity corresponding to areas of hemorrhage, also seen on panels D and E which show chronic blood byproducts on axial T2-weighted two-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 pre-contrast T1-weighted hyperintensity in on Panel G. Microhemorrhage is demonstrated on axial T2-weighted two-dimensional multi-echo 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.



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