CASE REPORT

Haemorrhagic conversion of infectious myelitis in an immunocompromised patient

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SUMMARY

A 28-year-old man recently diagnosed with HIV (CD4 19 cells/mm³, viral load 3.6 million copies/mL, not on highly active antiretroviral therapy on initial diagnosis at outside hospital), disseminated histoplasmosis, shingles and syphilis presented with paraplegia developing over 3 days. Spine MRI demonstrated a longitudinally extensive cord lesion extending from C3 to the tip of the conus. Brain MRI was consistent with meningoencephalitis. Cerebrospinal fluid findings were notable for positive varicella zoster virus (VZV) and cytomegalovirus (CMV) PCRs as well as a Venereal Disease Research Laboratory titre of 1:2. Patient was started on treatment for VZV and CMV meningoencephalitis, neurosyphilis and high-dose steroids for infectious myelitis. Repeat spine MRI demonstrated subacute intramedullary haemorrhage of the cervical cord. He was ultimately discharged to a skilled nursing facility for long-term intravenous antiviral therapy and rehabilitation. After 59 days in the hospital, his neurological exam remained grossly unchanged, with flaccid paraplegia and lack of sensation to fine touch in his lower extremities.

BACKGROUND

Myelopathies associated with a longitudinally extensive spinal cord lesion (LESCL) manifest as abnormal intramedullary signal extending over three or more vertebral segments on spine MRI.¹ They are often seen in the context of inflammatory or autoimmune processes, such as neuromyelitis optica spectrum disorders (NMOSDs), and in such instances are termed longitudinally extensive transverse myelitis. Myelopathies with LESCLs may have also been in neoplastic, vascular, infectious and traumatic aetiologies, as well as in the postvaccination setting.^{1 2} Haemorrhagic myelitis is relatively rare and, when observed, has been reported in the setting of varicella zoster virus (VZV) and herpes simplex virus-2 (HSV-2) infections in immunocompromised individuals.³ In the current report, we present a case of haemorrhagic conversion of infectious myelitis with an LESCL in an immunocompromised patient in the setting of central nervous system (CNS) infections related to VZV, cytomegalovirus (CMV) and neurosyphilis.

CASE PRESENTATION

A 28-year-old man with a history of HIV and AIDS (most recent CD4 count of 19 cells/mm³ and viral load of 3.6 million copies/mL) presented with acute

onset, progressively worsening weakness and loss of sensation of the lower extremities over a 3-day period and culminating in complete inability to move his lower extremities. Previous medical history is pertinent for a recent 3-week intensive care admission at an outside hospital where he was reported to have been started on highly active antiretroviral therapy (HAART) and diagnosed and treated for disseminated histoplasmosis, left hemithoracic shingles and syphilis.

Neurological exam demonstrated that the patient was alert and oriented to person and month, but neither place nor more specific information regarding time. Speech was preserved, and patient could follow simple commands. Cranial nerves II–XII were intact except for slightly decreased hearing bilaterally. Finger-to-nose was intact, but heel-to-shin test, gait and Romberg's test were unable to be assessed given patient's generalised weakness and bedridden state. Strength was 0/5 in both lower extremities. Patient demonstrated absent patellar and Achilles reflexes and bilateral positive Babinski's sign. Sensation to vibration was intact with decreased fine touch in the lower extremities.

INVESTIGATIONS

A non-contrast CT of the head was normal. A subsequent contrast-enhanced brain MRI demonstrated leptomeningeal enhancement with scattered supratentorial and infratentorial T2 hyperintense lesions consistent with meningoencephalitis (figure 1A). An MRI of the cervical, thoracic and lumbar spine demonstrated extensive abnormal intramedullary signal from C3 to the tip of the conus with associated cord expansion, consistent with an LESCL. Notable cerebrospinal fluid (CSF) findings from lumbar puncture included a positive PCR to VZV and CMV as well as a Venereal Disease Research Laboratory titre of 1:2. Work-up was negative for NMOSD (negative CSF and serum aquaporin-4 IgG). He was started on treatment for VZV and CMV meningoencephalitis, presumed CNS histoplasmosis infection as well as neurosyphilis with intravenous amphotericin, penicillin and ganciclovir. He was ultimately discharged to inpatient physical rehabilitation, but suffered a 3 min complex partial versus generalised seizure during his second day of his rehabilitation and was readmitted to the inpatient service.

A repeat brain MRI 12 days following the initial MRI exam demonstrated progression of the supratentorial and infratentorial brain parenchymal

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Figure 1 (A) Axial T2 fluid-attenuated inversion recovery imaging on presentation demonstrated nodular foci of hyperintensity centred in the frontal and temporal lobes as well as the midbrain. Abnormal leptomeningeal hyperintensity is located in the interpeduncular and perimesencephalic cisterns (white arrowheads). These findings are altogether consistent with meningoencephalitis. (B) Repeat imaging performed 12 days later demonstrates increased number of abnormal hyperintense foci scattered throughout the brain parenchyma, most notably in the deep grey and right temporal lobe. (C) Imaging performed 1 month following the initial MRI demonstrates less conspicuous and near-complete resolution of the lesions within the brain parenchyma and leptomeninges.

lesions ([figure 1B](#)) and increased leptomeningeal enhancement, reflecting progression of multifocal meningoencephalitis. A repeat cervical, thoracic and lumbar spine MRI demonstrated worsening cervical intramedullary signal abnormality and increased cervical cord expansion ([figure 2](#)). An intracranial magnetic resonance angiography without contrast was also performed and was normal.

Patient was started on levetiracetam (500mg every 12 hours) for his recent seizure as well as intravenous high-dose steroids (methylprednisolone 1g per day for 5 days, followed by dexamethasone 8mg every 12 hours for 11 days) for his myelopathy and a subsequent taper over 5 weeks (prednisone 80mg per day for 6 days, 60mg per day for 8 days, 40mg per day for 6 days, 30mg per day for 8 days and 10mg per day for 7 days) to doses treatable for possible immune reconstitution inflammatory syndrome (IRIS). Despite treatment, his neurological status

Figure 2 (A) Sagittal T1-weighted imaging of the cervical spinal cord without contrast or fat saturation does not demonstrate high signal to suggest subacute intramedullary haemorrhage. (B) Sagittal T2-weighted imaging of the cervical spinal cord without fat saturation demonstrates intramedullary high signal extending greater than three contiguous vertebral levels, consistent with a longitudinally extensive cord lesion. Note the associated marked expansion of the cord due to underlying oedema.

Figure 3 (A) Sagittal T1-weighted imaging of the cervical spine without contrast or fat saturation demonstrates a linear and central focus of intramedullary high signal extending from approximately C2 to C4 (white arrow), suggestive of presence of either intracellular or extracellular methaemoglobin seen in the subacute stages of haemorrhage. (B) Axial T1-weighted imaging of the cervical spine without contrast or fat saturation demonstrates the high-signal abnormality located within the central cord (white arrowhead).

further deteriorated with ascending weakness involving the bilateral upper extremities and culminating in flaccid paralysis.

A third brain MRI performed 2 weeks following initiation of steroid treatment demonstrated improvement in the multifocal supratentorial and infratentorial lesions ([figure 1C](#)). However, a third cervical spine MRI performed at the same time demonstrated a new linear focus of intrinsic T1 hyperintensity extending from C2 to C5 with persistent expansion of the cord at this level,

Figure 4 Sagittal T2-weighted imaging of the cervical spine without fat saturation continues to demonstrate high signal extending longitudinally throughout the expanded cord. The lack of low T2 signal suggests the absence of deoxyhaemoglobin (seen in the acute stage of haemorrhage) and, in combination with high signal on T1-weighted imaging, suggests that the intramedullary haemorrhage is within the late subacute stage.

consistent with late subacute intramedullary haemorrhage of the cervical cord (figures 3 and 4).

CSF findings from the initial lumbar puncture at the time of admission demonstrated xanthochromia, red cell count of 4125 cells/ μ L, white cell count of 32 cells/ μ L with lymphocytic predominance of 24%, glucose of 77 mg/dL and total protein of 757.8 mg/dL. CSF findings from a repeat lumbar puncture 12 days later also demonstrated xanthochromia, red cell count of 443 cells/ μ L, white cell count of 13 cells/ μ L with lymphocytic predominance of 78%, glucose of 102 mg/dL and total protein of 441.7 mg/dL.

Additional work-up of the CSF included a *Cryptococcus* antigen, enterovirus PCR and fungal and acid-fast bacilli cultures, which were all negative.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes trauma, anticoagulation/coagulopathy, spinal cord involvement by acute haemorrhagic leukoencephalopathy (AHLE), intramedullary cavernomas and arteriovenous malformations, primary spinal cord tumours such as ependymoma and spinal cord metastases.

Trauma may be excluded based on history. Anticoagulation and coagulopathy may be excluded based on coagulation tests as well as history. Underlying vascular and neoplastic lesions such as intramedullary cavernomas, arteriovenous malformations, primary spinal cord tumours such as ependymoma and spinal cord metastases were excluded based on the two initial MRIs prior to the onset of haematomyelia. Spinal cord involvement of AHLE may be excluded based on the absence of recent vaccination as well as the absence of coexisting asymmetrically distributed, white matter predominant brain parenchymal findings of AHLE/acute disseminated encephalomyelitis (ADEM).

TREATMENT

Throughout his 59-day hospital stay, patient received extended treatment for his VZV and CMV meningoencephalitis, initially receiving intravenous ganciclovir (5 mg/kg every 12 hours for 5 days, then 5 mg/kg every 12 hours for 2 days), which was changed to intravenous acyclovir (870 mg every 8 hours for 10 days, then 10 mg/kg every 8 hours for 26 days) and foscarnet (90 mg/kg every 12 hours for 13 days, followed by 7440 mg every 12 hours for 4 days, 7440 mg per day for 11 days, 90 mg/kg every 12 hours for 5 days and 90 mg/kg per day for 19 days) due to concern for myelosuppression.

He also received intravenous high-dose steroids initially for his myelopathy and a subsequent, extended taper for the possibility of IRIS (see the Investigations section regarding specific medication, frequency and duration).

The patient also completed 2 weeks of intravenous penicillin for neurosyphilis and remained on HAART and levetiracetam throughout his hospital stay. His HAART comprised one Genvoya tablet per day (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir 10 mg) for 17 days, then dolutegravir 50 mg per day for 38 days and one Truvada tablet (emtricitabine 200 mg and tenofovir 300 mg) per day for 42 days.

OUTCOME AND FOLLOW-UP

The patient remained seizure-free since the initial seizure episode prior to readmission and was ultimately discharged to an inpatient skilled nursing facility for long-term intravenous antiviral therapy as well as inpatient occupational and physical rehabilitation. After being on HAART for at least 59 days, his most recent CD4 count at the time of discharge remained

severely depressed at 10 cells/ mm^3 , and he continues to remain on HAART subsequent to discharge. At the time of discharge of his 59-day hospital stay, he demonstrated slight improvement in his neurological exam with a recovered 3/5 strength within his bilateral upper extremities, but persistent 0/5 strength with lack of sensation to fine touch in his lower extremities.

DISCUSSION

We describe an infectious myelitis with an LESCL complicated by intramedullary haemorrhage in an immunocompromised patient with coexisting CNS infections related to CMV, VZV and neurosyphilis.

Infectious causes of myelitis with an LESCL have included HSV, VZV, CMV, Epstein-Barr virus (EBV), HIV, human T lymphotropic virus-1, *Mycobacterium* spp, *Borrelia burgdorferi*, *Mycoplasma* spp, *Treponema pallidum* and *Schistosoma* spp.¹ A dermatomal skin eruption characteristic of VZV infection may not be seen in the immunocompromised, and CSF analysis is critical in the diagnosis of viral myelitis in these patients.¹⁴ Patients with an infectious myelitis present with CSF pleocytosis and positive PCR analysis and/or positive viral, bacterial or parasitic serologies. MRI findings of infectious myelitis with LESCLs vary based on the infectious agent, and many have overlapping features.⁵ When associated with skin findings, VZV has been described to cause intramedullary T2 signal hyperintensity and enhancement most significant at vertebral level of the affected dermatome.⁶ Both CMV and EBV infections are associated with enhancement of the nerve roots and leptomeninges; thickening and clumping of the roots may also be observed in CMV.⁶ HIV may cause either myelitis in conjunction with encephalitis or vacuolar myelopathy, the latter of which should be suspected if symptoms are of subacute onset and imaging shows prominent dorsolateral column involvement and T1 hypointense cysts.⁷ Bacterial causes, including *Mycobacterium tuberculosis* and *T. pallidum*, may cause leptomeningeal enhancement, with cord swelling and epidural enhancement associated with tuberculous myelitis.^{8,9} Neurocysticercosis of the spinal cord without signs of brain involvement is rare but would present with cystic and cavitary lesions. *Schistosoma* spp cause cord oedema and enhancement and favour the lumbar region and conus.^{10,11}

Haemorrhagic conversion of infectious myelitis is uncommon, and in our case, it was diagnosed based on the characteristic T1 shortening (hyperintensity) within the cervical cord typical of late subacute haemorrhage, as well as the red cell count and xanthochromia within the CSF on lumbar puncture. Haemorrhagic myelitis has thus far been reported in association with viral infections including VZV and HSV-2 and in predominantly immunocompromised individuals.^{12–14} More recently, a case of haemorrhagic myelitis in an immunocompetent patient has been reported following influenza vaccination.² Interestingly, while most prior reports of haemorrhagic myelitis have seemed to have occurred at presentation and near the time of hospital admission or diagnostic work-up, haemorrhagic conversion did not occur until more than 1 month following onset of symptoms and admission in our case. It may be important to make a distinction in cases in which haemorrhagic conversion occurs later. In our case, haemorrhagic conversion was not clinically apparent and was ultimately discovered at the subacute stage of haemorrhage during repeat imaging. Treatment of infectious myelitis without follow-up imaging may increase the risk of missing clinically occult haemorrhagic conversion, particularly if the clinician is unaware of the possibility of such a late complication in its natural history. Furthermore, it is possible that haemorrhagic conversion may have occurred later in the course in

our case as the patient was already on antiviral therapy for shingles prior to admission. His ongoing treatment prior to the onset of infectious myelitis may have delayed haemorrhagic conversion. As reported by Wang *et al*, their case haemorrhagic myelitis was initially misdiagnosed as a vascular malformation, which delayed antiviral treatment and was thought to be largely contributory to the poor outcome.³

Furthermore, while VZV CNS infection was confirmed based on CSF findings in our case, additional coexisting CNS infections involving CMV and *T. pallidum* were also present. To our knowledge, this is the first case in which haemorrhagic myelitis occurred in association with CMV CNS infection or neurosyphilis. In VZV infection, haemorrhage is postulated based on histopathological studies to be a result of small-vessel vasculitis and additionally as an immune restoration disease.^{3,4} Infections of the CNS by CMV and syphilis are also rarely associated with CNS vasculitis.^{15,16} It is unclear if these two coexisting infections may each have also contributed to the development of haemorrhagic myelitis. And if so, it is also unclear if it may be mediated similarly through a small-vessel vasculitis as observed in VZV myelitis.

Haemorrhagic conversion has also been observed to occur in AHLE, a relatively uncommon hyperacute form of ADEM, which is a postinfectious monophasic inflammatory demyelinating disorder.¹ However, spinal cord involvement in AHLE is unusual, although possible.^{1,2} In cases of AHLE, haemorrhage is thought to occur as a result of necrosis secondary to autoimmune vascular injury and perivascular demyelination.¹⁷ The previously reported associations of VZV infection, immunocompromised state and haemorrhagic myelitis argue against spinal cord AHLE involvement in the current case. Moreover, the asymmetrically distributed, white matter predominant abnormalities were absent.

Learning points

- ▶ Haemorrhagic myelitis is a rare entity most frequently observed in central nervous system infections by varicella zoster virus (VZV) or herpes simplex virus and particularly in the context of an immunocompromised state.
- ▶ MRI findings of the temporal evolution of intra-axial haematomas are characteristic and thus allow for confident diagnosis of the presence of intramedullary haemorrhagic conversion in infectious myelitis.
- ▶ Haemorrhagic myelitis in the case of VZV infection is postulated to be the result of a small-vessel vasculitis based on findings in histopathological studies.
- ▶ Haemorrhagic conversion of infectious myelitis may not necessarily occur until weeks following onset of myelitis and in spite of aggressive treatment.

In conclusion, intramedullary haemorrhagic conversion is an uncommon complication of infectious myelitis and may occur weeks following aggressive treatment and the onset of symptoms. Our case further corroborates the association of haemorrhagic myelitis with VZV CNS infection and an immunocompromised state as described previously in the literature and is also the first to report an association with neurosyphilis and CMV infections.

Contributors MSP, KYW and CML collected the data and drafted the manuscript. KYW, CML and MGR edited the paper. CML and KYW prepared the figures. All authors approved the final manuscript.

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