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CASE REPORT

Inflammatory flaccid myelitis in a patient with both anti-CRMP-5 IgG and CNS HIV escape

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SUMMARY

Anticollapsin-responsive mediator protein 5 (CRMP-5) IgG is an antibody generally associated with small-cell lung cancer, which is known to cause paraneoplastic neurological syndromes, including encephalitis, myelitis and neuropathy. HIV escape is a phenomenon in which a patient with low or undetectable levels of HIV RNA in plasma is found to have elevated levels in cerebrospinal fluid (CSF). We present a case of a 58-year-old HIV-positive woman with undetectable plasma viral load who developed a subacute flaccid paraparesis. Over the course of 4 months, she had a broad inflammatory and infectious workup that was unrevealing until repeat imaging showed an inflammatory myelitis. Workup was notable for elevated HIV RNA copies in CSF, as well as anti-CRMP-5 autoantibodies in serum. Despite changing her antiretroviral therapy and multiple modalities of immunomodulation, the patient failed to respond adequately to treatment. This case illustrates a complex clinical picture with a unique presentation of anti-CRMP-5 myelitis.

BACKGROUND

Collapsin-responsive mediator protein 5 (CRMP-5) is a synaptic protein that is implicated in paraneoplastic syndromes associated with small-cell lung carcinoma (77% of cases) and thymoma (6%).[1] Its presentation can include a variety of neurological disorders, including encephalopathy, myelopathy, radiculopathy, optic neuropathy and chorea.[1] This is the first report of CRMP-5-mediated myelitis in the context of HIV infection.

Early in HIV infection, cerebrospinal fluid (CSF) infection is equilibrated with plasma infection, but localised amplification can result in compartmentalisation of populations of viruses in the CSF that differ from plasma populations. Over time, M-tropic R5 viruses that infect macrophages (unlike T-tropic viruses that infect T cells predominantly early in disease) can evolve in CSF. These are suspected to be linked to the development of central nervous system (CNS) disease.[2] As such, rarely, patients with HIV on antiretroviral therapy (ART) with suppressed plasma HIV viral loads can present with 'CNS escape', in which the CNS infection may no longer be susceptible to their ART as a result of a different population developing in the CNS.[2 3] Symptomatic CNS escape is associated with CSF pleiocytosis.[3]

Manifestations of HIV in the spinal cord include vacuolar myelopathy and HIV myelitis, and distinction between these two entities is vital. While vacuolar myelopathy is a non-inflammatory vacuolation predominantly of the lateral and posterior white matter by lipid-laden macrophages, HIV myelitis is a more acute and very rare inflammatory condition associated with CSF pleiocytosis, which is considered to be directly attributable to HIV infection, although poorly understood.[4 5]

We describe a patient with a clinical course that was more subacute than is typical for a primary inflammatory HIV myelitis. Further testing revealed both CNS HIV escape and, later, anti-CRMP-5 IgG antibodies in CSF. Suspicion of inflammatory myelitis due to HIV led to a delay in diagnosis and definitive treatment of the antibody-mediated disorder, with attendant poor clinical outcome.

CASE PRESENTATION

A 58-year-old African–American woman with a history of well-controlled HIV and history of breast cancer and hepatitis C presented to the emergency department with papilledema. Neuroimaging was normal and CSF analysis showed pleiocytosis but no other abnormalities. Two months prior to the development of papilledema, she underwent a change in her ART (from cobicistat–elvitegravir–emtricitabine–tenofovir alafenamide+atazanavir to darunavir–cobicistat+emtricitabine tenofovir alafenamide) due to adverse effects.

The patient re-presented within a month with subacute back pain and began developing progressive bilateral lower extremity weakness to the point that she stopped ambulating. She had no sensory changes aside from pain in the upper back and in the lower back and legs. She had begun to use a diaper due to impaired mobility but retained control of urination and bowel movements. This prompted several hospital admissions for failure to thrive, despite repeated serial MRI studies with gadolinium of the brain and spine revealing no acute abnormalities. Figure 1 summarises the timeline of clinical events.

Four months following her initial symptoms, the patient presented again to the emergency department; examination was notable for no observed movement at rest in the bilateral lower extremities. With encouragement, she provided a flicker of unsustained movement in the hip flexors, abductors, adductors and great toe flexion. She was intermittently tearful but alert, oriented in detail and conversant. Cranial nerve testing did not reveal any deficits, and there was no papilledema at this time.

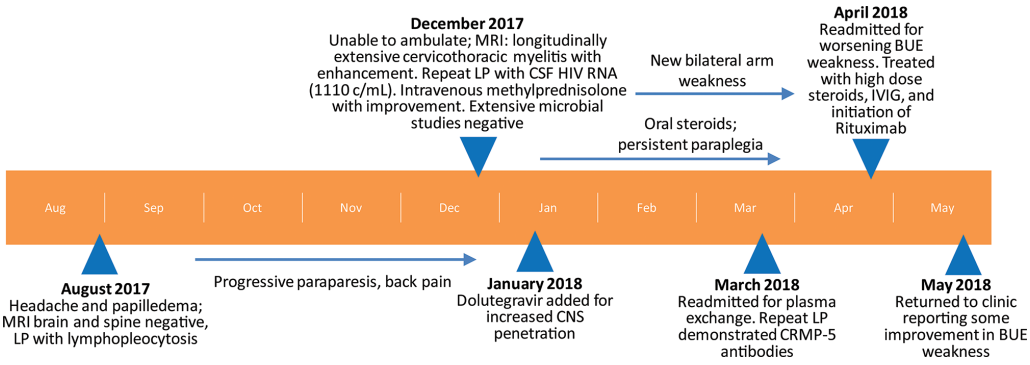

Figure 1 Timeline of the patient's pertinent clinical events and diagnostic results. BUE, bilateral upper extremities; CNS, central nervous system; CRMP-5, collapsin-responsive mediator protein 5; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; LP, lumbar punctures.

Sensory examination was equal and symmetric in all modalities. Reflexes were normal, equal and symmetric, though her toes were noted to be intermittently upgoing. Coordination was intact in the upper extremities. She was not able to walk.

This examination was clearly different from an examination with neurology 1 month previously, where she was noted to have 4+/5 strength throughout the lower extremities (limited due to effort and pain) without other objective findings.

During the course of her illness, she had a total of three lumbar punctures, all of which demonstrated CSF pleiocytosis (88%–98% lymphocytes) but were otherwise unremarkable in more specific infectious and neoplastic studies. Her workup also included broad-serum studies, notable for an elevated antinuclear antibody level.

INVESTIGATIONS

Despite previous spinal MRIs being unrevealing, an MRI spine survey without and with contrast was repeated and now demonstrated diffuse longitudinal cord oedema and patchy enhancement, greatest along the lateral spinal tracts, from the cervicomedullary junction to the distal cord at L1 (figure 2). Additionally, mild compression of the ventral cord at C3–C4 due to spinal stenosis was noted and unchanged from previous imaging.

Further workup revealed a CD4 level of 379 with HIV-1 RNA undetectable in serum. Antinuclear antibodies were significantly elevated with a titre of >1:640 in a speckled pattern.

Analysis of the CSF included total red blood cells of 360, total white blood cells of 86 (12% macrophages and 86% lymphocytes (65% small T cells and 18% small mature B cells)), protein level of 353 mg/dL, glucose level of 101 mg/dL and lactate concentration of 4.3 mmol/L. Opening pressure was not obtained due to positioning in a technically difficult procedure.

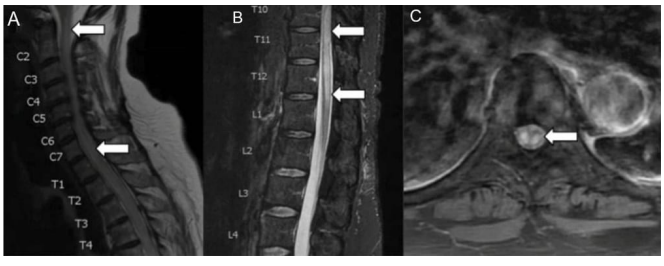

Figure 2 Sagittal T2-weighted MRI image without contrast demonstrating cord oedema (open arrows) in the cervical (A) and thoracic (B) spinal cord. An axial image (C) in the thoracic cord demonstrates the involvement of the lateral tracts.

CSF HIV RNA quantitative PCR was elevated at 1110 copies/mL and 3.05 log copies/mL.

Anti-CRMP-5 IgG antibody, as part of a serum paraneoplastic encephalomyelitis panel, returned positive several weeks after the above testing, with no other autoantibodies detected. CT of the chest, abdomen and pelvis with contrast were negative for evidence of malignancy.

Other negative or unrevealing serological studies included creatine phosphokinase, anti-ribonucleoprotein, anti-double-stranded DNA, anti-Smith, anti-Jo, anti-aquaporin-4, C3, C4, aldolase, ACE and *Bartonella henselae* IgG/IgM, *Brucella* antibody, human T-lymphotrophic (HTLV) I/II antibody, mumps IgG/IgM and measles IgG/IgM. Negative CSF studies included ACE, veneral disease research laboratory (VDRL) test, *Escherichia coli* K1 PCR, *Haemophilus influenzae* PCR, *Listeria monocytogenes* PCR, *Neisseria meningitides* PCR, *Streptococcus agalactiae* PCR, *S. pneuomoniae* PCR, cytomegalovirus PCR, enterovirus PCR, herpes simplex virus 1 and 2 PCR, human-herpes virus 6 PCR, varicella zoster virus PCR, John Cunningham virus (JCV) PCR, *parechovirus* PCR, *Cryptococcus neoformans* PCR, West Nile virus IgG/IgM, California encephalitis IgG/IgM, St. Louis encephalitis IgG/IgM, Eastern equine encephalitis IgG/IgM, Western equine encephalitis IgG/IgM, HTLV I/II ELISA, cytology and flow cytometry (prior to receiving steroids).

DIFFERENTIAL DIAGNOSIS

Among the initial concerns included neuromyelitis optica spectrum disorder or other demyelinating disease; infectious processes; malignancy, such as lymphoma or glioma; or other inflammatory conditions, such as sarcoidosis. When the patient's CSF HIV viral load returned elevated without evidence of other infections, a preliminary diagnosis of HIV-related inflammatory myelopathy with escape was suggested; however, this was considered less likely after her anti-CRMP-5 antibody returned elevated.

TREATMENT

When her CSF HIV RNA returned elevated, dolutegravir was added due to concern for resistant HIV within the CNS. CSF HIV RNA remained detectable at 180 copies/mL, and 2 months later, etravirine was added to specifically target M-tropic R5 HIV.

After her MRI showed new spinal cord oedema, the patient was started empirically on 1000 mg methylprednisolone daily for 3 days followed by a slow taper of oral steroids. Her pain improved without appreciable change in her neurological exam. Her anti-CRMP-5 IgG returned later, at which point she was treated with two courses of plasma exchange. Despite this, her symptoms progressed, and she developed weakness in the arms

and respiratory weakness. She was treated with intravenous immunoglobulin and, ultimately, rituximab without clinical improvement. Most recently, she was started on mycophenolate mofetil.

OUTCOME AND FOLLOW-UP

At the time of diagnosis, our patient had endured approximately 4 months of back pain and mild leg weakness, progressing to flaccid paraplegia. She had radiographic improvement transiently in response to steroids but soon developed weakness in the arms, despite escalating doses. At her most recent follow-up appointment (approximately 10 months after her diagnosis), she remains quadriparetic and fully dependent on caregivers for all activities of daily living.

DISCUSSION

A review of the published literature revealed no reported cases of CRMP-5 antibody-mediated neurological disease in HIV. Given the presence of CRMP-5 antibodies in CSF with chronic progressive flaccid myelitis and presumed optic neuritis followed by no response to antiretroviral intensification for CSF escape, we believe the CRMP-5 antibodies are responsible for her clinical disease. However, a causal relationship cannot be definitively confirmed. The most likely explanation for CSF escape is that the inflammatory response to the CRMP-5 autoantibody amplified HIV replication in the CNS, as has been seen in other disorders causing pleiocytosis.[6] In a patient with no known malignancy, it is not clear why she was at risk of CRMP-5-associated myelitis and whether her HIV predisposed her to this, as there have been no previous cases reported of a CRMP-5-mediated neurological syndrome in the setting of HIV.

Despite aggressive immunotherapy, our patient failed to make a significant clinical improvement. CRMP-5-associated neurological disorders, in general, are poorly responsive to treatment.[1] It also remains possible that despite an extensive radiographic search for underlying malignancy, she may have a neoplasm that is thus far too small to detect and continues to stimulate anti-CRMP-5 antibody production.

This is the first documented case of CRMP-5-associated myelitis masquerading as an HIV escape phenomenon to our knowledge. It illustrates the need for exhaustive testing to arrive at a final diagnosis to best guide treatment and prognosis.

Learning points

- Cerebrospinal fluid HIV escape describes the finding of elevated HIV RNA with low or undetectable titres in the serum.
- HIV escape may or may not be associated with HIV-related central nervous system disease, and further testing may be necessary to reach a final diagnosis.
- CRMP-5 antibodies generally are associated with neoplasms but should be considered in patients with HIV who present with inflammatory myelitis.

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