Clinical Problem-Solving: Fever and Rapidly Progressive Weakness in an Immunocompromised Patient

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Abstract

Here we report the challenging case of a 41-year-old man with HIV complicated by AIDS and a history of prior neurologic injury from progressive multifocal leukoencephalopathy who presented with headache, fevers, lower extremity weakness, hyperreflexic upper extremities, and diminished lower extremity reflexes. We review the clinical decision-making and differential diagnosis for this presentation as the physical examination evolved and diagnostic testing changed over time.

Case Presentation

A 41-year-old man with a history of HIV/AIDS and prior progressive multifocal leukoencephalopathy (PML) involving the cerebellum and pons presented in the early fall with 1 day of fever, headache, and lower extremity weakness. The patient's history was significant for working outdoors during the summer in the midwestern United States. The day prior to presentation, the patient developed fever, holocephalic dull headache, back pain, and mild bilateral lower extremity weakness. Over the next 12 hours, his weakness progressed to an inability to walk, prompting presentation to the emergency department.

Upon presentation, he was febrile (38.9°C) and mildly tachycardic (108 beats per minute (BPM)). The remainder of his general medical examination was unremarkable. On initial neurologic examination, he had symmetrically weak lower extremities (Medical Research Council grade 2/5 proximally and 4-/5 distally) with reduced but present reflexes in his lower extremities and normal strength with hyperreflexia in his upper extremities. Sensation including the perineal region was normal. He had reduced negative inspiratory force and forced vital capacity measurements. Cognition and language were unaffected.

As with any neurologic presentation, it is important to establish a likely localization for pathology within the central or peripheral nervous system. The initial clinical picture of acute-onset bilateral lower extremity weakness can be seen with both acute neuropathic disorders and acute spinal cord conditions. The reflex examination is typically used to

distinguish neuropathic from spinal cord conditions. This patient had marked discordance between the upper and the lower extremities, opposite of what is typically seen in spinal cord lesions. Neuropathic conditions lead to loss of reflexes, while the opposite is seen with spinal injury. However, the reflex examination can be misleading early in the disease course. Early in acute neuropathies reflexes may still be present while with acute spinal cord disease, reflexes may be diminished. In this case, the history of PML further complicated interpretation of the examination findings because it was difficult to distinguish a change in reflexes relative to a presumed abnormal baseline. Typically, a neuropathic process would result in either pain or loss of sensation in the limbs, while a sensory level is frequently observed in spinal cord processes. Our patient had retained limb sensation and no overt sensory level. This suggested that our patient either had a developing condition or an acute pure motor syndrome.

We opted to build our initial differential diagnosis around a spinal cord localization, although the patient's examination did not fit this localization in the classic manner. We did so to evaluate the patient for spinal cord disorders that require emergent treatment. Included in this group of conditions are abscess, vascular malformations, extrinsic spinal cord compression, and spinal cord ischemia. We also considered

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Figure 1. A, Day 1 sagittal T1-weighted postcontrast MRI sequence of thoracic and lumbar spine. B, Axial T1-weighted postcontrast MRI images of the cauda equine and nerve roots. Day 7 images demonstrate epidural and nerve root enhancement (white arrowheads) not present on day 1. MRI indicates magnetic resonance imaging.

diagnoses particularly relevant to immunocompromised patients with HIV including vacuolar myelopathy, central nervous system lymphoma, toxoplasmosis, mycobacterial myelopathy, recurrent progressive multifocal leukoencephalopathy (PML), and cryptococcus. Conditions known to cause acute myelopathy in both immune competent and compromised patients were also considered including herpes simplex (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), enterovirus, syphilis, and human T cell lymphotropic virus (HTLV). The subacute autoimmune conditions of multiple sclerosis, neuromyelitis optica, and idiopathic transverse myelitis were considered as were B12 and copper deficiency as causes of chronic myelopathy.

To narrow the differential diagnosis and to exclude processes that would require emergent surgical intervention, our patient underwent urgent whole spinal cord magnetic resonance imaging (MRI) with contrast. When considering spinal cord imaging, it is wise to recognize that whole spinal cord imaging can be difficult for patients to tolerate because of the length of the study, and imaging a select region of the spinal cord may result in higher quality images. When selecting a region of the spine to image, one can omit regions below a sensory or motor level (ie, a lesion causing arm weakness *must* be in the cervical spine or higher) but not above. In this patient, the weakness and diminished reflexes in the legs could be due to either an evolving process in the cauda equina (lumbar spine) or an acute process in the cervical or thoracic spine; therefore, the entire cord was imaged. In addition to routine blood work, we assessed the patient's CD4 T cell count. We planned to perform a lumbar puncture as soon as imaging confirmed that the patient's symptoms were not due to an obvious structural lesion or abscess.

Routine blood tests including basic metabolic panel, complete blood count, hepatic function, and coagulation tests were within normal limits. The patient's CD4 count was 207 cells/ μ L. An initial MRI of the brain and cervical, thoracic, and lumbar spine revealed no evidence of trauma, mass, bleeding, or clear pathologic contrast enhancement (Figure 1). Cerebrospinal fluid examination revealed a lymphocytic pleocytosis (172 nucleated cells, 63% lymphocytes) with elevated protein (63mg/dL) and normal glucose. Cerebrospinal fluid (CSF) bacterial and fungal cultures were negative. Given the concern for a viral etiology, multiple CSF viral studies were tested including HSV, VZV, CMV, HTLV, and enterovirus, all of which were negative. Epstein Barr Virus and JC virus studies were also negative. The patient was briefly treated with vancomycin, ceftriaxone, ampicillin, and acyclovir based solely upon the lumbar puncture/CSF profile. The patient's presentation was not consistent with bacterial meningitis; thus, the antibiotics were discontinued as soon as cultures returned negative. Acyclovir was similarly discontinued after the CSF polymerase chain reaction for HSV was negative.

Over the next 3 days, the patient's leg weakness progressed to flaccid paralysis with loss of patellar and ankle reflexes. Over the next week, he developed bilateral arm weakness, trunk weakness, urinary retention, and decreased rectal tone before clinically stabilizing. His sensory and mental status examinations remained intact.

Our initial myelopathy-based localization and differential diagnosis did include conditions in which spasticity is not a strong feature; however, the timeline of their evolution did not fit the pattern of what our patient was experiencing. The progressive loss of deep tendon reflexes in addition to the

ascending pattern of weakness suggested a condition such as Guillian-Barre syndrome (GBS). However, GBS most commonly features sensory loss and may be marked by autonomic instability which our patient did not experience. There is a variant of GBS termed acute motor axonal neuropathy (AMAN) that is a common presentation in the far East and in developing countries, but is considered uncommon in most areas of the United States. Additionally, the GBS/AMAN CSF profile is characterized by a albuminocytologic dissociation of low cell count and elevated protein. Our patient had a CSF pleocytosis in the range typical of viral syndromes.

An alternate localization for flaccid paralysis with retained sensation besides motor nerves is the anterior horn cells. This possibility seemed plausible as the patient's MRI was unremarkable. Thus, we expanded our differential diagnosis to include poliomyelitis and enterovirus D68 and 71 syndromes. Given the time of year the patient presented, his work as a landscaper and the infectious prodrome, West Nile Virus (WNV) was considered a leading candidate. *Borrelia burgdorferi* was also considered but is not typical in the region of presentation.

Given the dual localization of flaccid paralysis and recognizing that imaging changes can lag behind clinical changes, we decided to repeat spinal cord imaging. We also decided that nerve conduction studies and electromyography would be helpful to distinguish weakness localized to either the spinal cord or the peripheral nerves.

Magnetic resonance imaging of the entire spine was repeated on hospital day 7. This showed diffuse contrast enhancement of the ventral nerve roots from T12 through L5 as well as extensive epidural enhancement (Figure 1). Nerve conduction studies (NCS) performed on days 10 and 17 after symptom onset demonstrated progressive loss of Compound Muscle Action Potential (CMAP) amplitudes with normal conduction velocities without conduction block. Sensory nerve responses were normal. Needle electromyography (EMG) showed fibrillation and sharp wave potentials with reduced recruitment and normal appearing motor unit action potentials (MUAP). The electrodiagnostic studies in combination with the normal sensory clinical examination localized the patient's weakness to either the ventral nerve roots or the anterior horn cells. West Nile Virus immunoglobulin (Ig) G (IgG) and IgM CSF titers were negative tested by enzyme-linked immunosorbent assay (ELISA). In light of the unrevealing infectious disease workup, we decided to offer the patient empiric immunomodulatory treatment with 5 g intravenous methylprednisolone followed by 5 cycles of plasma exchange.

Although the patient was undergoing diagnostic testing and waiting for results, the team had to contend with the daily reality of a justifiably concerned patient and his family wondering whether there was treatment for the patient's condition. The team needed to decide whether or when to try empiric

treatment for a presumed immune/inflammatory root, motor nerve, or anterior horn cell process. Electrodiagnostics alone do not distinguish those possibilities. After the infectious workup was negative, we felt the risk to benefit ratio of empiric immunomodulatory therapy was in favor of empiric treatment. We weighed the treatment options based upon the remaining differential diagnosis, ultimately basing treatment upon a spinal cord localization. Steroids are a first-line therapy for inflammatory myelopathies regardless of cause. The follow-up therapy with plasma exchange was similarly selected based upon our primary concern for an inflammatory myelopathy being ultimately responsible for the patient's condition.

A portion of the initial CSF sample was sent to the state public health laboratory for additional arbovirus testing. This was positive for West Nile IgM by microsphere immunoassay. A summary of all initial laboratory results is shown in Table 1.

Follow-up examination 5 months after presentation showed minimal motor recovery. The patient required full assistance for transfers and had asymmetric upper extremity weakness with a normal sensory examination. Deep tendon reflexes were reduced but present in the upper extremities and absent in the lower extremities. Repeat MRI showed resolution of the previous nerve root and epidural enhancement as well as extensive paraspinal muscle atrophy. Repeat electrodiagnostic studies demonstrated severe denervation in the legs and mild denervation in the arms consistent with a motor neuronopathy. Follow-up examination 18 months after initial presentation still showed flaccid lower extremity weakness, but truncal and arm strength were improved sufficiently, so the patient can assist with his transfers to and from a manual wheelchair. He has adapted to his disability with hand controls for a modified van allowing him a degree of self-reliance and freedom.

This is an illuminating case of neuro invasive WNV presenting with acute flaccid paralysis (AFP). The case included several unique diagnostic challenges including a baseline neurologic deficit in an immunodeficient patient, an atypical presentation, and a false-negative WNV serology. The case illustrates the value of serial imaging and electrodiagnostics, especially in cases with an evolving examination. In this case, serial imaging and a high index of suspicion led to repeat WNV testing which confirmed the diagnosis.

West Nile Virus is a zoonotic arbovirus of the Flaviviridae family transmitted to humans via mosquitos usually during the summer months.^{1,2} The first cases in the United States occurred in 1999. There is now a stable pattern of endemic infection with intermittent spikes in disease occurrence. The majority of WNV infection cases are asymptomatic; however, approximately 20% of WNV patients develop a flu-like febrile illness. Less than 1% of all WNV infections are neuroinvasive.³ West Nile Virus neuroinvasive disease takes 3 main

Table 1. Summary of Serum and CSF Analysis.

Blood Counts	Value
White blood cell count	7.7 K/mm ³
Hemoglobin	14.4 g/dL
Hematocrit	43.50%
Platelets	226 K/mm ³
CD4 count	24% (207 cells/ μ L)
Serum chemistry	
Sodium	137 mm/L
Potassium	4.4 mm/L
Chloride	101 mm/L
Carbon dioxide	22 mm/L
BUN	14 mg/dL
Creatinine	1.18 mg/dL
Glucose	118 mg/dL
Calcium	9.6 mg/dL
Aspartate transaminase	45 Units/L
Alanine transaminase	25 Units/L
Alkaline phosphatase	62 Units/L
Vitamin B12	418 pg/mL
Erythrocyte sedimentation rate	9 mm/h
C-reactive protein	0.4 mg/L
Serum and urine infectious studies	
HTLV antibody	Negative
Hepatitis C RNA	Negative
Urine histoplasma antigen	Negative
Mycoplasma antibody	Negative
CSF Profile	
Protein	63 mg/dL
Glucose	77 mg/dL
Red blood cells	0 cells/ μ L
Nucleated cells	172 cells/ μ L (12% neutrophils, 61% lymphocytes, 22% monocytes)
CSF infectious studies	
VDRL	Negative
Varicella zoster virus PCR	Negative
Herpes simplex virus I PCR	Negative
Cytomegalovirus PCR	Negative
Ebstein-barr virus PCR	Negative
JC virus PCR	Negative
Aerobic bacterial culture	Negative
Fungal culture	Negative
Acid-fast bacilli culture	Negative
Cryptococcus antigen	Negative
Paraneoplastic panel	Negative
West Nile IgG and IgM	Initially negative subsequently IgM positive

Abbreviations: BUN, urea nitrogen; CSF, cerebrospinal fluid; HTLV, human T cell lymphotropic virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; VDRL, venereal disease research laboratory test.

forms: meningitis, encephalitis, and AFP.⁴ Acute flaccid paralysis typically presents in the first 24 to 48 hours of the illness with acute onset of limb weakness and hypo or areflexia.^{1,4} The weakness is usually asymmetric and may involve the facial nerve.⁴ Sensory changes may be seen but are atypical and not usually severe.⁵ West Nile Virus AFP can occur in isolation or with WNV encephalitis.¹ There remains

no Food and Drug Administration-approved treatment for WNV in the United States. Intravenous Immunoglobulin collected from regions with endemic WNV has been investigated as a potential treatment option for neuroinvasive WNV⁶ but has not consistently demonstrated effectiveness.⁷

This patient's presentation was atypical because of his symmetric weakness. This was further confounded by his baseline upper extremity hyperreflexia from prior cerebellopontine PML. This initial feature of his examination increased concern for autoimmune myelopathic process. As his examination progressed to flaccid paralysis, the localization possibilities included acute neuropathy, nerve root and anterior horn cell lesions, and necrotic/vacuolar myelopathy. The diagnostic workup for suspected WNV AFP includes CSF analysis, MRI, and electrodiagnostic evaluation.⁸⁻¹⁰ The CSF is usually characterized by pleocytosis with elevated protein, and WNV IgM is present in CSF by day 7 in 95% of patients.³ In our patient, CSF analysis revealed a lymphocytic pleocytosis with mildly elevated protein. Initial CSF WNV IgG and IgM detection by ELISA was negative, but repeat testing via microsphere immunoassay was positive. The microsphere assay utilizes recombinant WNV envelope (E) protein antigen covalently coupled to fluorescent polystyrene microspheres. Patient serum or CSF that binds the E protein antigen is then detected with fluorescent labeled antihuman immunoglobulin antibody using flow cytometry. The assay is a well-validated test for WNV and related flavi-viruses and may have increased sensitivity.¹¹ CSF in our patient was obtained the morning after initial presentation, prior to the development of maximal weakness and imaging changes, thus CSF antibody levels were presumably too low for the detection with standard ELISA-based testing.

Idiopathic Guillain-Barre syndrome must be included on the differential in patients with ascending weakness, areflexia, negative infectious serologies, and nerve root enhancement on MRI. Although GBS is not typically associated with a CSF pleocytosis, mild CSF pleocytosis has been observed in individuals with HIV.¹² Serial electrodiagnostic and imaging studies were helpful to localize the site of pathology to the motor nerve roots or anterior horn cells (although these would not necessarily distinguish it from the GBS variant AMAN). Prior work has demonstrated that anterior horn cells appear to be the primary target in WNV AFP.⁹ As such we hypothesize that the contrast-enhancing nerve roots observed with the day 7 MRI represents the upstream damage to the anterior horn cells more than a radiculopathy, especially considering his spared sensory examination.

In summary, the patient's evolving examination, lymphocytic pleocytosis, transient ventral nerve root enhancement, and motor neuron loss on EMG/NCS fit a diagnosis of an infectious process involving motor nerve roots/anterior horn cells. The clinical course and performed tests motivated a high index of suspicion, and ultimately repeat WNV testing with microsphere immunoassay confirmed the diagnosis. This case illustrates the value of serial imaging and

electrodiagnostics in WNV AFP as well as the value of pursuing repeat or alternative CSF testing in cases where the clinical index of suspicion is high.

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References

1. Davis LE, DeBiasi R, Goade DE, et al. West Nile virus neuroinvasive disease. *Ann Neurol*. 2006;60(3):286-300. doi:10.1002/ana.20959.
2. Leis AA, Stokic DS. Neuromuscular manifestations of West Nile virus infection. *Front Neurol*. 2012;3:37. doi:10.3389/fneur.2012.00037.
3. DeBiasi RL, Tyler KL. West Nile virus meningoencephalitis. *Nat Clin Pract Neurol*. 2006;2(5):264-275. doi:10.1038/ncpneuro0176.
4. Sejvar JJ. Clinical manifestations and outcomes of West Nile virus infection. *Viruses*. 2014;6(2):606-623. doi:10.3390/v6020606.
5. Sejvar JJ, Leis AA, Stokic DS, et al. Acute flaccid paralysis and West Nile virus infection. *Emerg Infect Dis*. 2003;9(7):788-793. doi:10.3201/eid0907.030129.
6. Shimon Z, Bin H, Bulvik S, et al. The clinical response of West Nile virus neuroinvasive disease to intravenous immunoglobulin therapy. *Clin Pract*. 2012;2(1):e18. doi:10.4081/cp.2012.e18.
7. Hart J, Tillman G, Kraut MA, et al; NIAID Collaborative Antiviral Study Group West Nile Virus 210 Protocol Team. West Nile virus neuroinvasive disease: neurological manifestations and prospective longitudinal outcomes. *BMC Infect Dis*. 2014;14:248. doi:10.1186/1471-2334-14-248.
8. Park M, Hui JS, Bartt RE. Acute anterior radiculitis associated with West Nile virus infection. *J Neurol Neurosurg Psychiatry*. 2003;74(6):823-825.
9. Marciniak C, Rosenfeld EL. Serial electrodiagnostic studies in West Nile virus-associated acute flaccid paralysis. *Am J Phys Med Rehabil*. 2005;84(11):904-910. doi:10.1097/01.phm.0000184160.87895.ea.
10. Leis AA, Stokic DS, Webb RM, Slavinski SA, Fratkin J. Clinical spectrum of muscle weakness in human West Nile virus infection. *Muscle Nerve*. 2003;28(3):302-308. doi:10.1002/mus.10440.
11. Wong SJ, Demarest VL, Boyle RH, et al. Detection of human anti-flavivirus antibodies with a West Nile virus recombinant antigen microsphere immunoassay: detection of human anti-flavivirus antibodies with a West Nile virus recombinant antigen microsphere immunoassay. *J Clin Microbiol*. 2004;42(1):65-72. doi:10.1128/JCM.42.1.65.
12. Brannagan TH 3rd, Zhou Y. HIV-associated Guillain-Barré syndrome. *J Neurol Sci*. 2003;208(1-2):39-42. doi:10.1016/S0022-510X(02)00418-5.