CLINICAL PRACTICE

*Exercises in Clinical Reasoning***An HIV-Positive Patient with Back Pain: Too Many Choices**

Cecilia T. Costiniuk, MD, MSc, FRCPC¹, Feras M. Ghazawi, PhD, MSc, M.D. C.M. (c)², and Stephen Kravcik, MD, MSc, FRCPC^{3,4}

¹Division of Infectious Diseases, Department of Medicine, University of Ottawa, Ottawa, Canada; ²Faculty of Medicine, McGill University, Montreal, Quebec, Canada; ³Division of General Internal Medicine, Department of Medicine, University of Ottawa, Ottawa, Canada;

⁴Ottawa Hospital-General Campus, Ottawa, Ontario, Canada.

J Gen Intern Med 29(4):680–4

DOI: 10.1007/s11606-013-2742-4

© Society of General Internal Medicine 2014

In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (bold). Additional commentary on the diagnostic reasoning process (*italics*) is integrated throughout the discussion.

A 57-year-old, human immunodeficiency virus (HIV)-infected male presented with a 2-month history of progressive lower back discomfort accompanied by left leg weakness and right thigh and calf cramping. He was not on HIV antiretroviral (ARV) therapy; his most recent CD4 count was 169 cells/μL (normal range, 628–1698) and his viral load (VL) was 146,207 copies/mL.

This man's low back pain with lower extremity weakness and cramping most importantly suggests the possibility of cauda equina syndrome or spinal root compression. For the sake of completeness, I would like to know whether he has any bowel or bladder symptoms, or any sensory symptoms. As well, I would like to know whether his weakness is progressive, and whether there are aggravating or alleviating factors. If the pain is slowly progressive, the differential diagnosis is quite broad, and neoplastic disease of the spinal cord and extrinsic compression by epidural or intradural tumor may present in this manner. Demyelinating, degenerative and metabolic or deficiency disease may present in this way as well.

Here, an initial problem presentation is construed. The clinician is formulating a hypothesis that could account for this man's presentation. By eliciting further elements of the patient's history, the clinician is assembling information that will either uphold or discredit this

hypothesis. The clinician is attempting to determine whether this man has any symptoms suggestive of cauda equina syndrome, which is a medical emergency requiring urgent surgical intervention. The list of etiologies causing spinal root compression or other spinal cord processes is quite extensive, although the chronicity of the presentation will help narrow the list.

The back discomfort and leg weakness came on gradually. There was no past history of back symptoms or injury. He denied any bowel incontinence, although he had been constipated for a few weeks. Over the 1 to 2 weeks following his initial presentation, he developed urinary urgency and urge incontinence, but denied any sexual difficulties, postural headache or dizziness. Apart from the back pain, he denied any history of numbness, tingling or paresthesias in his limbs. Similarly, there was no history of any numbness or sensory loss in his sacral area.

In any middle-aged male regardless of HIV seropositivity, spinal cord compression from malignancy, infection or intervertebral disk herniation must be considered. Malignancies common in a male over 50, regardless of HIV serostatus, include metastatic disease from prostate cancer, lung cancer and colon cancer, as well as multiple myeloma. Lung and colon cancer may also be associated with paraneoplastic disorders that can, in turn, affect the spinal cord. I would ask about the presence of B symptoms, smoking, dyspnea and change in bowel habits. Other infections that are not necessarily HIV-associated, such as bacterial abscess secondary to seeding from bacteremia, or herpes simplex virus (HSV), can also present with spinal cord symptoms. These may occur in both immunocompetent and immunocompromised hosts. Other infections, such as Toxoplasmosis and JC virus, can also cause myelitis, but are most often seen in immunosuppressed hosts. Tuberculous infection of the spine with secondary cord compression is a possibility, so I would ask about risk factors for, and symptoms of, tuberculosis. HIV-infected individuals are more likely to have virtually all the infections that would present with spinal root compression symptoms.

Here the clinician continues to gather further historical information in order to prioritize his differential diagnoses.

Received June 16, 2013

Revised September 5, 2013

Accepted December 5, 2013

Published online January 7, 2014

The clinician has also invoked various illness scripts or mental models of disease. These mental representations of disease serve as a reference for pattern recognition, and enable the clinician to scrutinize the patient presentation to identify the similarities and differences between cases.¹ Furthermore, despite the fact that the individual has HIV infection, the clinician first considers possible conditions unrelated to HIV infection, and then considers possible conditions to which the individual may be predisposed due to his HIV infection.

Although this patient had lost 5 kg over the past 6 months, he denied any fevers, chills or sweats. Moreover, he denied any history of smoking, hemoptysis or chronic cough. He denied lymphadenopathy, early satiety or B symptoms. This patient was born in Haiti, although the timing of his acquisition of HIV infection was unknown. He was diagnosed with HIV in 1999, at which time his Mantoux skin test was negative. Although he had been on antiretrovirals between 1999 and 2001, he had not been on any antiretrovirals for over 10 years. As he had been feeling well, he did not seek medical care for routine monitoring of his HIV infection.

The lack of constitutional symptoms and presence of weight loss help little in narrowing the differential diagnosis. The weight loss may suggest malignancy, but is consistent with untreated advanced HIV infection. Malignant or non-malignant spinal root compression, or less likely, intrinsic spinal cord disease must still be ruled out. Physical examination should help localize the lesion to the spinal cord and direct imaging, which should be pursued quickly. However, at this point, it is still imperative to consider common bacterial causes of central nervous system (CNS) infection, even in the absence of constitutional symptoms. Furthermore, given that this patient is HIV-infected and originates from Haiti, tuberculosis (TB) could still be a possibility and would fit with the slowly progressive course of his illness. Greater than 10 % of all extrapulmonary tuberculosis manifests as bone and joint infections.² However, given the lack of constitutional symptoms, TB or another chronic infection seems less likely, and this patient's overall probability of TB infection is moderate.

Here the clinician recognizes the importance of epidemiological information and this helped refine the differential diagnosis. Furthermore, by still considering diagnoses such as extrapulmonary tuberculosis, despite the absence of systemic symptoms commonly associated with this condition, the clinician avoids "confirmation bias," whereby data are gathered or interpreted to support a hypothesis rather than disprove it.³

His cardiovascular, respiratory, abdominal, lymph node and dermatological exam were all within normal limits. Mental status and cranial nerve examination were normal. He had normal strength, sensation and coordination of the upper limbs, although he was

slightly hyperreflexic with 3+/4 reflexes bilaterally. There was no Hoffman sign. There was no sensory level over his abdomen and no tenderness over his spine. Examination of his legs revealed diffuse mild weakness, especially on the left. His tone was increased and his reflexes were 3+/4 bilaterally, with a few beats of clonus at the ankles. The plantar response was upgoing bilaterally. There was no muscle wasting or fasciculations. Pinprick sensation was reduced below the ankles and proprioception and vibration sense in his toes were reduced. His gait was slightly wide-based, unsteady and slightly spastic. He favoured the left leg while ambulating. Romberg's sign was positive.

This patient's physical exam is most consistent with a myelopathy. In determining the etiology of a myelopathy, three key pieces of information should be elicited. These include the chronicity of onset of symptoms and whether there is a history of pain and/or trauma. Pain of rapid onset may be due to vascular etiologies, such as spinal cord infarction or from bleeding into a spinal cord tumor.⁴ Stepwise increases in pain are also consistent with vascular etiologies.⁴ Other conditions associated with pain of rapid onset include vertebral fractures, where herniation of bone into the epidural space can ensue. In contrast, enlargement of a mass occurs at a relatively slower pace.⁴ When myelopathy is painless with a slow rate of onset, the differential diagnosis remains broad and can still include neoplastic diseases, in addition to degenerative diseases, demyelinating diseases, nutrient deficiency and spondylosis. Both vitamin B12 deficiency and tabes dorsalis, a form of tertiary neurosyphilis, may manifest with combined spinal cord and peripheral nerve disease. However, at this moment, imaging is imperative to rule out spinal cord compression.

Magnetic resonance imaging (MRI) of the brain and spine with gadolinium did not reveal any explanation for the patient's bilateral leg weakness and spasticity. There was no abnormal cord signal that could suggest an intrinsic myelopathy or abnormal enhancement with gadolinium. The only finding was some minor degenerative disk disease in the lower lumbar spine. Chest x-ray was unremarkable.

This patient's MRI rules out structural conditions as a cause of his progressive spastic weakness. The focus should now turn towards investigations for possible non-structural causes of his signs and symptoms. These include vitamin B12 deficiency, as well as infectious etiologies like syphilis and HIV myelopathy. He is from the Caribbean, so human T cell lymphotropic virus (HTLV)-1-associated myelopathy (HAM or tropical spastic paraparesis [TSP]) should be considered as well. Although B12 deficiency is more common in HIV-infected persons, it would be worthwhile to confirm whether he has other risk factors for this (personal or family history of autoimmune disease, gastric

surgery, or small bowel disease). It would be important to ask about a history of sexually transmitted infections (STIs), suggesting risk for syphilis. Finally, copper deficiency can lead to an ataxic myelopathy, but is extremely rare.

In the context of immunosuppression, infections that can rarely affect the spinal cord include toxoplasmosis, varicella zoster virus (VZV) and cytomegalovirus (CMV); these would require cerebrospinal fluid (CSF) examination for diagnosis. JC virus infection causing progressive multifocal leukoencephalopathy (PML) is also possible, but should have been evident on the MRI. Moreover, although uncommon, schistosomiasis can also present with acute or subacute myelopathy when the spinal cord is involved.⁵ I would therefore like to know when he left Haiti and whether he has had any travel there in the past 6 years or so. Syphilis also remains on the differential diagnosis at this point. Similarly, HIV myelopathy is another consideration, although this often presents at a later stage in the course of HIV infection.

Here the clinician demonstrates an appreciation for the relative prevalence of disease. For example, although a potential etiology of myelopathy, the clinician recognizes that this is rare, and thus the pre-test probability of this etiology is low. Here the clinician also avoids “base-rate neglect,” whereby the true prevalence of disease is not appropriately considered.⁶ Furthermore, although the individual originated from Haiti, the clinician obtains further epidemiological details, such as by asking whether he has had any recent travel, as this will also influence the prioritization of differential diagnoses, as certain infections are less likely to be the cause of present illness if there was no recent travel.

He denied further risk factors for vitamin B12 deficiency and had no history of non-HIV STIs. Complete blood count (including MCV), electrolytes and extended electrolytes were all within normal limits. Erythrocyte sedimentation rate (ESR) was elevated at 98 mm/h (normal range, 0–6) although his C-reactive protein (CRP) was normal, <0.2 mg/mL (normal range, <10.0). Serum protein electrophoresis demonstrated a diffuse hypergammaglobulinemia with no abnormal bands. The serum vitamin B12 level was low at 74 pmol/L (normal range, 133–675). Given his low B12 level, he was immediately started on intramuscular vitamin B12 replacement.

Low serum vitamin B12 levels, likely due to reduced absorption, are common in HIV-infected persons.⁷ Although B12 deficiency is common in HIV-infected patients,⁷ it is important to rule out other conditions that could be present simultaneously and that could also be contributing to the signs and symptoms experienced by this patient. Further testing for syphilis and HTLV-1 are mandatory.

Syphilis testing revealed positive screen (T. pallidum IgG/IgM chemiluminescent microparticle immunoassay (CMIA)) and confirmatory tests (Treponema pallidum particle agglutination assay [TP-PA]), but a negative rapid plasma reagin (RPR) screen; he had no past clinical history of syphilis and testing was negative some 10 years earlier. HTLV-1 testing by enzyme immunoassay (EIA) and Line Immunoassay were reactive.

So there are now three, and possibly four, causes of his myelopathy: vitamin B12 deficiency, neurosyphilis, HAM and HIV myelopathy. B12 deficiency may improve with vitamin replacement and HIV myelopathy may settle with effective antiretroviral therapy. Otherwise, CSF analysis may be useful; detectable RPR, elevated protein or pleocytosis would be consistent with neurosyphilis, whereas detection of HTLV-1 would be consistent with HTLV-1 associated myopathy.

Here the clinician is examining various possibilities and these conditions may coexist together. This enables the clinician to avoid “anchoring bias,” whereby one commits to a diagnosis and does not re-evaluate the diagnosis upon receipt of inconsistent data.⁶ The clinician is also using a test of treatment, namely vitamin B12 replacement and antiretroviral therapy, to help determine whether this patient’s myelopathy could be due to B12 deficiency and HIV, respectively. As B12 replacement therapy is generally very safe, the clinician would have a low threshold for instituting this treatment. With regards to his HIV, antiretroviral therapy is indicated in this patient anyways. Improvement in the patient’s symptoms with treatment implies that at least one of these etiologies were implicated in this patient’s symptoms.

CSF analysis demonstrated a WBC count of 23×10^6 cells/mL with a lymphocytic predominance. Glucose was normal. Protein was slightly elevated at 0.6 g/L (normal range 0.15–0.45). CSF was negative for syphilis reagin as well as cryptococcal antigen, toxoplasma antibody and CMV, VZV and HSV DNA by polymerase chain reaction (PCR). HTLV-1/2 EIA screen was reactive, with HTLV line immunoassay reactive for HTLV-1, but negative for HTLV-2.

The patient was started on tenofovir/emtricitabine, etravirine and ritonavir-boosted darunavir for HIV, with complete and sustained virologic suppression, and continued B12 replacement. He was treated for late latent syphilis with three doses of IM benzathine penicillin. His weakness transiently improved slightly, but in spite of HIV suppression and vitamin B12 replenishment, his neurological status thereafter gradually worsened, with slowly worsening leg weakness.

He has retired from his employment as a truck driver because of difficulty entering and leaving his vehicle, and is under the care of a rehabilitation specialist to allow him to function optimally with his disability.

Given that his neurological status worsened in spite of HIV suppression and vitamin B12 replenishment, this suggests his myelopathy was primarily related to HTLV-1, possibly with a component of HIV myelopathy that responded to therapy. However, some data suggests that HTLV-1 may respond to nucleoside reverse transcriptase inhibitor therapy, which may have explained the transient improvement.⁸

Response to ARVs is often used as a diagnostic clue, given that biopsies for the sole purpose of diagnosing HIV myelopathy are frequently not performed.

COMMENTARY

A common dilemma physicians encounter involves determining when more than one diagnosis is possible. This is especially true in the modern medical era, whereby patients have become increasingly complex and a vast array of diagnostic tests are available.⁹ In these cases, we often consider host factors, such as age and immune status, in addition to the degree of match between disease characteristics and mental models in order to decide whether we lean towards one diagnosis or accept two or more diagnoses. In this case, the patient has advanced HIV infection. As alluded to earlier, this patient is therefore at risk not only of conditions afflicting men over 50 years in general, but also those conditions observed in predominantly immunocompromised individuals.

The concept of thresholds plays a central role in the decision-making process. Physicians have a spectrum of thresholds for various diseases. Severity and treatability influence the height of these thresholds.¹⁰ Thresholds exist for both diagnostic testing (“testing thresholds”) and treatment (“test-treatment”), and these thresholds can be given values from information based on the reliability and potential risks of the test, in addition to the benefits and risks of a specific treatment.¹¹ As cauda equina syndrome is a medical emergency requiring urgent surgical intervention, the physician in this case had a low threshold for ordering imaging to exclude the condition. Furthermore, given the higher incidence of syphilis among HIV patients, the physician had a low threshold for ordering syphilis screening as well.

In this case, the “test of treatment” was used in an attempt to decipher among possible diagnoses.

A test of treatment helps to make a diagnosis when characteristics of a case are atypical, to see if a treatment is effective in someone with a known illness, and to aid in deciphering among different possible diagnoses.¹¹ This latter situation applies to the current case, as the decision was made to treat the patient for his B12 deficiency, HIV and syphilis. All of these conditions are treatable, the therapies are relatively safe (B12 injections and Penicillin) and the alternative of withholding treatment in someone

who does have these conditions can result in serious adverse sequelae. Therefore, a physician would typically have low a treatment threshold for testing for, and treating, these conditions.

In clinical medicine, we often search for diagnostic parsimony. Centuries ago, William Occam was credited for encouraging us to select among the simplest hypothesis when there are competing hypotheses in what is referred to as “Occam’s razor”.⁹ However, as discussed by Hilliard et al., in the modern medical era, it may often be appropriate to invoke the concept of “Saint’s triad.” Although this triad consists of hiatal hernia, gallbladder disease and diverticulosis,⁹ it was named after the surgeon who recognized that more than one illness could account for a patient’s signs and symptoms.⁹ With regards to the patient in this case, as previously alluded to, the fact that his neurological status worsened in spite of antiretrovirals and B12 supplementation suggests that his myelopathy was primarily related to HTLV-1, possibly with a component of myelopathy that responded to treatment.

CLINICAL TEACHING POINTS

1. HTLV-1 is transmitted by blood products, organ transplantation, sexual contact and breast milk. Human T-cell Lymphotropic Virus (HTLV)-1-endemic regions include the Caribbean basin (2.4–5.7 %) and central Africa (up to 3.2 %).¹²
2. Although the vast majority of individuals harbouring HTLV infection remain asymptomatic carriers, approximately 0.3–4 % of individuals will develop disease at some point in their lives.^{12,13} Individuals with TSP classically present with back and leg pain followed by ambulatory impairment and urinary dysfunction due to a spastic bladder.¹³ Clinical exam reveals symmetric spasticity and weakness predominantly affecting the lower extremities, as well as bilateral Babinski signs. HTLV myelopathy is often, but not always, associated with a negative MRI. The MRI is usually normal, but may show atrophy of the thoracic cord.¹⁴ Other conditions associated with HTLV-1 infection include adult T cell leukemia/lymphoma (ATL) and opportunistic infections such as *Strongyloides stercoralis* infection and hyperinfection.¹⁵
3. Diagnosis requires clinical evidence of myelopathy coupled with the presence of HTLV antibody in serum or cerebrospinal fluid.
4. Although the true impact of HTLV-1 and HIV coinfection remains unclear, infection with one of these viruses appears to increase one’s risk of acquiring the other. Furthermore, although HTLV-1 coinfection may delay HIV progression, it may also increase the risk of developing neurodegenerative diseases like TSP.¹⁵

5. While there is no proven therapy for TSP, HIV-infected individuals should be on antiretroviral therapy. Corticosteroids may provide temporary relief of symptoms.^{12,13}

Acknowledgements: Cecilia T. Costiniuk has received a Canadian HIV Trials Network (CTN) Fellowship.

Conflict of Interest: The authors declare that they do not have a conflict of interest.

Corresponding Author: Stephen Kravcik, MD, MSc, FRCPC; Ottawa Hospital-General Campus, L2I37, 501 Smyth Road, Ottawa, Ontario, Canada K1H 8 L6 (e-mail: skravcik@toh.on.ca).

REFERENCES

1. Coderre S, Mandin H, Harasym PH, Fick GH. Diagnostic reasoning strategies and diagnostic success. *Med Educ*. 2003;37(8):695-703.
2. Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of extrapulmonary tuberculosis in the United States, 1993-2006. *Clin Infect Dis*. 2009;49(9):1350-7. doi:10.1086/605559.
3. Nickerson RS. Confirmation Bias: A Ubiquitous Phenomenon in Many Guises. *Rev Gen Psychol*. 1998;2(2):175-220. doi:10.1037/1089-2680.2.2.175.
4. Seidenwurm DJ. Neuroendocrine imaging. *Am J Neuroradiol*. 2008;29(3):613-5.
5. Nascimento-Carvalho CM, Moreno-Carvalho OA. Neuroschistosomiasis due to *Schistosoma mansoni*: a review of pathogenesis, clinical syndromes and diagnostic approaches. *Revista do Instituto de Medicina Tropical de Sao Paulo*. 2005;47(4):179-84.
6. Croskerry P. The importance of cognitive errors in diagnosis and strategies to minimize them. *Acad Med*. 2003;78(8):775-80.
7. Hepburn MJ, Dyal K, Runser LA, Barfield RL, Hepburn LM, Fraser SL. Low serum vitamin B12 levels in an outpatient HIV-infected population. *International journal of STD & AIDS*. 2004;15(2):127-33. doi:10.1258/095646204322764334.
8. Taylor GP, Hall SE, Navarrete S, Michie CA, Davis R, Witkover AD, et al. Effect of lamivudine on human T-cell leukemia virus type 1 (HTLV-1) DNA copy number, T-cell phenotype, and anti-tax cytotoxic T-cell frequency in patients with HTLV-1-associated myelopathy. *J Virol*. 1999;73(12):10289-95.
9. Hilliard AA, Weinberger SE, Tierney LM Jr, Midthun DE, Saint S. Clinical problem-solving. Occam's razor versus Saint's Triad. *New Engl J Med*. 2004;350(6):599-603. doi:10.1056/NEJMcps031794.
10. Glasziou P, Rose P, Heneghan C, Balla J. Diagnosis using "test of treatment". *BMJ*. 2009;338:b1312. doi:10.1136/bmj.b1312.
11. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *New Engl J Med*. 1980;302(20):1109-17. doi:10.1056/NEJM198005153022003.
12. Grindstaff P, Gruener G. The peripheral nervous system complications of HTLV-1 myelopathy (HAM/TSP) syndromes. *Semin Neurol*. 2005;25(3):315-27. doi:10.1055/s-2005-917668.
13. Berger JR, Sabet A. Infectious myelopathies. *Semin Neurol*. 2002;22(2):133-42. doi:10.1055/s-2002-36536.
14. Orland JR, Engstrom J, Fridley J, Sacher RA, Smith JW, Nass C, et al. Prevalence and clinical features of HTLV neurologic disease in the HTLV Outcomes Study. *Neurology*. 2003;61(11):1588-94.
15. Verdonck K, Gonzalez E, Van Dooren S, Vandamme AM, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. *Lancet Infect Dis*. 2007;7(4):266-81. doi:10.1016/S1473-3099(07)70081-6.