Journal of NeuroVirology, 15: 282–287, 2009

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280902913263

informa
healthcare

Case report

Coxsackie B meningoencephalitis in a patient with acquired immunodeficiency syndrome and a multiple sclerosis–like illness

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Both Coxsackie infection and multiple sclerosis (MS) are rare in human immunodeficiency virus (HIV) infection. We report a 35-year-old woman with known HIV infection of 12 years' duration and a clinical illness of 4 years' duration consistent with MS. The latter was characterized by optic neuritis, bilateral abducens palsies, recurrent Bell's palsy, hemiparesis, and ataxia coupled with white matter abnormalities on magnetic resonance imaging (MRI). Autopsy revealed Coxsackie B meningoencephalitis; no other infectious disease were detected and no histopathological features of MS were evident. We suggest that the relapsing-remitting neurological disease in this patient was the consequence of Coxsackie B meningoencephalitis. This is the first case report, to the best of our knowledge, of an enteroviral meningoencephalitis complicating human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). *Journal of NeuroVirology* (2009) **15,** 282–287.

Keywords: AIDS; HIV, Coxsackie B; HIV; meningoencephalitis; multiple sclerosis

Background

Although both humoral and cellular immunity are important in the clearance of coxsackieviruses, clinically symptomatic infection with this small, nonenveloped RNA virus is rare in human immunodeficiency (HIV) infection. Its relative absence in the setting of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) attests to the importance of preserved elements of the immune system. In one study of the cerebrospinal fluid (CSF) of patients with neurological disease employing reverse transcriptase–polymerase chain reaction (RT-PCR), enterovirus was not observed in any of 39 AIDS patients with encephalitis, aseptic meningitis, myeloradiculitis, polyradiculitis, retinitis, or ventriculitis, yet enteroviruses were the most commonly detected virus in the immunocompetent population (Casas *et al,* 1999). With respect to enterovirus-related neurological disease in HIV/AIDS, there has been but one case of severe rhabdomyolysis attributed to Coxsackie B (Beressi *et al*, 1994), and, to the best of our knowledge, no recognized cases of meningoencephalitis.

Similarly, multiple sclerosis (MS) or a MS-like condition occurring with HIV/AIDS is a rare occurrence (Berger *et al,* 1989; Gray *et al,* 1991; Berger *et al,* 1992; Graber *et al,* 2000; Facchini *et al,* 2002; Duran *et al,* 2004; Coban *et al,* 2007). In the small number of instances in which brain tissue has been examined, histopathological examination reveals demyelination with relatively preserved axons, foamy macrophages, reactive astrocytes, and perivascular inflammation consistent with the diagnosis of MS (Berger *et al,* 1989; Gray *et al,* 1991; Graber *et al,* 2000). We present a patient with HIV infection and a MS-like condition in whom autopsy demonstrated a lymphocytic meningoencephalitis due to Coxsackie B. No other infections were detected and there were no histopathological

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The authors would like to acknowledge the support of Ventana Medical Systems (Tucson, AZ) for providing the Ultraview Ultrasensitive Red System.

Received 17 November 2008; revised 23 December 2008; accepted 28 January 2009.

features suggestive of MS despite careful tissue examination. We suggest that chronic Coxsackie B meningoencephalitis was responsible for the neurological disorder.

Case report

This 35-year-old female with AIDS presented to our institution in June 2007 for management of a neurologic disorder. She had been found to be seropositive for HIV in 1995 and started on antiretroviral therapy (ART) in 1997. Prior to the institution of ART, her CD4 count had been as low as 88 cells/mm^3 and she had experienced several AIDS-related illnesses, including oral thrush and shingles.

Neurological symptoms first developed in 2003 with a right Bell's palsy that almost completely resolved in the ensuing months. In 2005, she developed horizontal diplopia consequent to bilateral sixth nerve palsies, bilateral impaired visual acuity, slurred speech, impaired coordination, imbalance, and generalized facial and limb weakness and numbness. A bout of thoracic zoster occurred shortly after the onset of these symptoms. Within 6 months of the appearance of the neurological symptoms, they had largely resolved. Later in the year, she developed left-sided Bell's palsy. Neurological examination in 2006 showed left peripheral facial weakness and right upper extremity weakness and numbness, which slowly resolved over 6 months.

At the time of examination in June 2007, she reported excessive fatigue for which she received modafinil 200 mg daily, Lhermitte's phenomenon, intermittent diplopia, and facial numbness, right-sided high-pitched tinnitus, generalized weakness, poor balance, enervation on heat exposure, and urinary frequency and urgency for which she was taking Detrol LA 4 mg daily. Antiretroviral medication included atazanavir, didanosine, tenofovir, and ritonavir. Detailed physical and neurological examinations were remarkable for pale optic discs, impaired color vision, downbeat and coarse horizontal nystagmus with abnormal smooth pursuit movements bilaterally, subtle left peripheral facial weakness, brisk muscle stretch reflexes and brisk jaw jerk, impaired vibratory and position sense in distal lower extremities, positive Romberg, and abnormal tandem gait. Her CD4 count at presentation was 666/μl and HIV viral load was undetectable. Magnetic resonance imaging (MRI) of the brain showed large hyperintense lesions in the deep white matter bilaterally (Figure 1A and B). Lumbar puncture showed a 8 white blood cells (WBCs)/μl, protein 92 mg/dl (normal: 40–70 mg/dl), glucose 52 mg/dl (15–40 mg/dl), five oligoclonal bands, and normal myelin basic protein. Visual-evoked potentials revealed a prolongation of the P100 bilaterally. Brainstem-evoked potentials demonstrated a right central conduction delay. Median and tibial somatosensory-evoked potentials were normal. A diagnosis of multiple sclerosis in the setting of HIV infection was made and glatiramer acetate (Copaxone) 20 mg subcutaneously daily was initiated. At the follow-up visit in September 2007, she complained of muscle cramping, but no other new symptoms. Gabapentin was initiated.

In December 2007, she developed a progressive, bifrontal headache. Two weeks later, she presented with confusion and was admitted for further evaluation. Examination showed a waxing and waning mental state, bilateral papilledema, bilateral horizontal nystagmus with poor pursuit, a peripheral left facial weakness, impaired coordination in her arms (greater on the left), brisk reflexes, and bilateral extensor plantar responses. An MRI of the brain revealed progression of the diffuse hyperintense lesions previously seen on FLAIR and T2 imaging (Figure 1C and D). These were not evident on T1-weighted imaging and did not contrast enhance. Lumbar puncture showed an opening pressure of 33 mm H_2O, 25 WBCs/μl (95% lymphocytes, 4% monocytes, 1% neutrophils), protein 129 ml/dl, glucose 56 mg/dl, lactate dehydrogenase (LDH) 13 U/L (<20 U/L), and lactate 1.8 mmol/L (1.1–2.4 mmol/L). Bacterial, fungal, and viral cultures revealed no growth. CSF cryptococcal antigen and Venereal Disease Research Laboratory (VDRL) tests were negative. Polymerase chain reaction (PCR) for JC virus, toxoplasma, cytomegalovirus, herpes simplex virus, varicella-zoster virus, and Epstein-Barr virus were negative. An electroencephalogram revealed bihemispheric slowing and frontal intermittent rhythmic delta activity. CD4 count was 443/μl and the HIV viral load was 85 copies/ml. Serum Lyme titers, VDRL, angiotension-converting enzyme, cytomegalovirus PCR, and toxoplasmosis titers were unremarkable. Repeat lumber puncture 1 week after presentation and 1 day before the biopsy had unchanged findings. On December 17, 2007, meningeal and brain biopsies were performed. Following surgery, the patient became unresponsive and died. Head computed tomography was consistent with postoperative changes and diffuse cerebral edema with transtentorial herniation.

At autopsy, gross examination of the brain was remarkable for tonsillar and uncal herniation. Severe edema was noted on microscopic examination. There was significant perivascular cuffing with prominent reactive lymphocytes without evidence of neoplastic transformation. Microglial nodules were evident and perivascular lymphocytes with parenchymal extension were present in gray matter, white matter, and meninges (Figure 2A to D), but no multinucleated giant cells were seen. The parenchymal inflammation was associated with reactive astrocytosis. There were no Cowdry-type inclusions observed. No histopathological features of progressive multifocal leukodystrophy

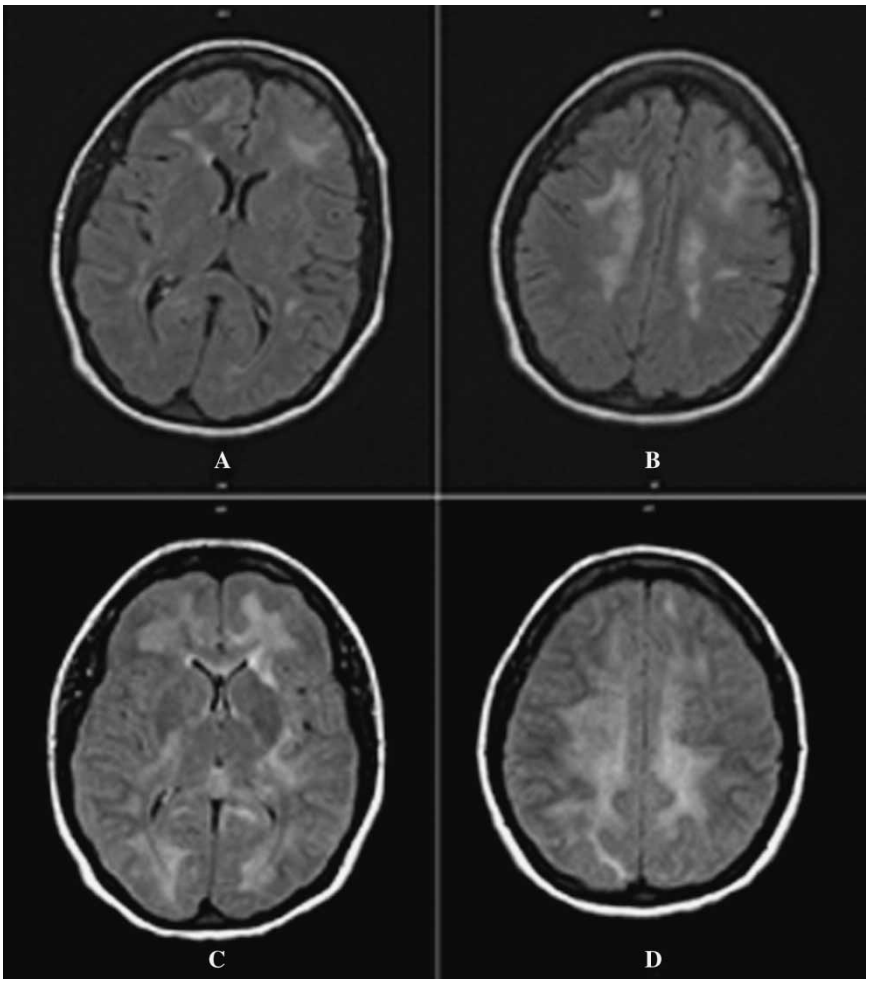

Figure 1 Brain MRIs from June 2007 (**A** and **B**) and December 2007 (**C** and **D**). Fluid-attenuated inversion recovery sequence images on MRI from June 2007 (**A** and **B**) show diffuse hyperintense signal abnormalities in both cerebral hemispheres. A repeat (**C** and **D**) in December 2007 shows that these lesions are more extensive.

(PML) were observed; cultures and stains for microorganisms, including gram, Giemsa, *Toxoplasma*, JC virus, cytomegalovirus, Epstein-Barr virus, and acid-fast for *Mycobacteria*, were negative. JC virus PCR on the tissue was negative. Immunohistochemical labeling (including CD20, CD79, CD15, CD4, CD3, MIB-1, kappa/lambda) revealed no evidence of lymphoma. Neither the surgical biopsy nor the autopsy tissue showed pathological changes consistent with demyelinating disease. The pathological diagnosis was lymphocytic meningoencephalitis. Outside the central nervous system (CNS), there was focal acute bronchopneumonia (probably not linked to CNS findings) and no other specific findings.

Tissue obtained from the frontal cortex, both gray and white matter, was examined by immunohistochemistry and real-time *in situ* PCR. Both techniques revealed evidence of Coxsackie B present in cells with cytologic features of neurons. Immunohistochemistry was performed with the Ultraview Ultrasensitive Red system from Ventana Medical Systems (Tucson, AZ). Using cases of serology and/or RT-PCR–confirmed enteroviral myocarditis as controls, antibody was optimized from Dako (Carpinteria, CA), clone 5-D8/1. Optimal conditions included no pretreatment and a dilution of 1:20. This antibody reacts with an epitope on the VP1 peptide, which is highly conserved within the enterovirus group. Originally generated using Coxsackie B5 as immunogen, this antibody reacts with most of the enterovirus strains of the Coxsackie, echovirus, and poliovirus groups. No reaction is seen with a range of other RNA viruses, including human rotavirus, yellow fever virus, measles virus, and rhinovirus A1. The counterstain was hematoxylin and the signal red (Figure 2E and F). Negative controls included omission of the primary antibody and brain tissues from patients without any clinical evidence of viral disease that were shown to be negative for enteroviral by RT PCR-based on *in situ* analysis.

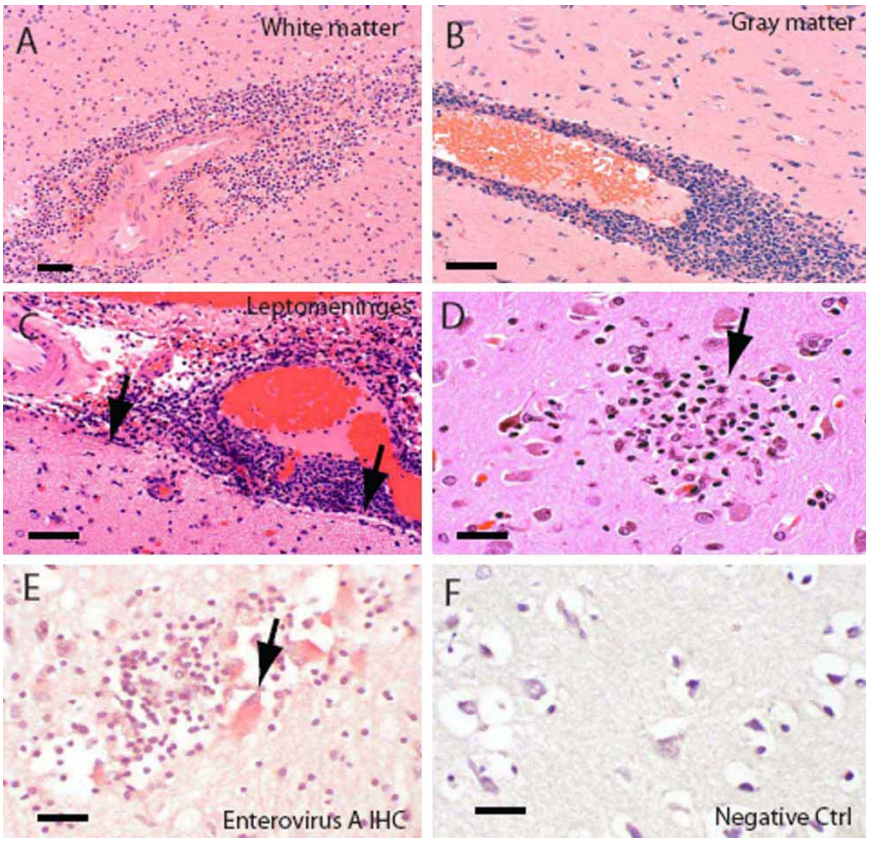

Figure 2 Brain histopathology from autopsy tissue (frontal lobe). Sections of brain showed lymphoplasmacytic infiltrates in white matter (**A**), gray matter (**B**), and meninges (**C**). Pial surface in **C** shown with arrows. Note the prominent perivascular mononuclear infiltrates. Also seen were collections of cells similar to 'microglial nodules' in brain parenchyma (**D**, *arrow*). Immunocytochemistry for entertovirus A was positive (**E**, *arrow*), as shown by red-stained cells. Negative control (**F**) showed no staining. Scale bars equal 200 microns (**A**–**C**) and 100 microns (**D**–**F**).

The real-time *in situ* PCR protocol has been previously described (Nuovo, 2008). Briefly, optimal protease digestion time was determined using non-specific incorporation of the reporter nucleotide digoxigenin dUTP. Optimal protease digestion was followed by overnight incubation in RNase-free DNase (10 U per sample; Boehringer Mannheim, Indianapolis, IN) and one-step RT/PCR using the rTth system and digoxigenin dUTP. The chromogen is nitroblue tetrazolium and 5-bromo-4-chloro-3-indolyl-phosphate (NBT/BCIP), with nuclear fast red as the counterstain. The primer sequences for coxsackievirus were CCCCGGACTGAGTATCAATA and GCAGTTAGGATTAGCCGCAT (Altschul *et al,* 1997). These primers are specific for most of the Coxsackie B serotypes and a few of the Coxsackie A serotype cDNA as per the BLAST sequence analysis of the National Center of Biotechnology Information database. Negative controls for viral cDNA-based signal included the omission of primers, the use of echovirus specific primers, and a normal brain section. Electron microscopy was not performed on the tissue.

Discussion

In contrast to prior reports of MS with HIV/AIDS in which brain pathology was consistent with the former diagnosis, our patient displayed a leptomeningitis, but no evidence of demyelination at autopsy. Diagnosing MS in the setting of HIV/AIDS can be perplexing. Commonalities of both disorders include hyperintense signal abnormalities on magnetic resonance imaging (Whiteman *et al,* 1997) and elevated CSF immunoglobulin G (IgG) and the presence of CSF oligoclonal bands (Singer *et al,* 1997) Brainstem auditory-evoked potentials may show an increase in I-V interpeak latencies over time in HIV, although other interval latencies remain are normal (Hall *et al,* 1997); however, visual-evoked potentials in HIV are typically normal (Hall *et al,* 1997). Our patient fulfilled the diagnostic criteria for multiple sclerosis (Polman *et al,* 2005), exhibiting relapsing-remitting focal neurological symptoms and signs implicating disease in the optic nerves, brain, brainstem, and spinal cord. White matter hyperintensities were observed on T2-weighted

and FLAIR MRIs, the visual-evoked and brainstem auditory-evoked potentials were abnormal, and the CSF showed elevated oligoclonal bands. Although fulfilling clinical diagnostic criteria for MS, this diagnosis was incorrect. Therefore, caution needs to be exercised in using ancillary parameters in the diagnosis of MS in the setting of HIV/AIDS.

Bell's palsy is a well-described neurological complication of HIV infection and our patient's initial neurological presentation may have simply been a reflection of that disorder (Brown *et al,* 1988). Similarly, some of her other neurological findings, including impaired vibratory and position sense, abnormal Romberg, poor tandem gait, and extensor plantar responses may also be ascribable to HIV involvement of peripheral nerves and spinal cord (Berger and Levy 1993). However, certain neurological features, including optic nerve disease, downbeat nystagmus, and Lhermitte's phenomenon, would be distinctly unusual with HIV infection. Coupled with the MRI findings, abnormal CSF and abnormal evoked potentials, MS occurring in association with HIV was the leading diagnostic consideration.

MS or an MS-like condition in the setting of HIV infection has been previously reported (Berger *et al,* 1989; Gray *et al,* 1991; Berger *et al,* 1992; Graber *et al,* 2000; Facchini *et al,* 2002; Duran *et al,* 2004; Coban *et al,* 2007). Whether the frequency of this association exceeds that expected in the HIV/AIDS population remains to be determined. This is the first case, to the best of our knowledge, in which a virus other than HIV has been demonstrated in the brain with an MS-like illness accompanying HIV infection. Whether the immune reconstitution inflammatory syndrome (IRIS) (Shelburne *et al,* 2002) contributed to the clinical syndrome observed terminally remains uncertain, but seems unlikely. Arguing against IRIS is the fact that she had been on effective highly active antiretroviral therapy (HAART) for years and had CD4 count exceeding 400 cells/mm^3 and low or undetectable HIV viral loads during this period.

On rare occasion, coxsackieviruses may cause severe neurological disease. A fatal encephalitis lethargica picture attributed to Coxsackie B4 developed in a 33-year-old woman with Henoch-Schonlein purpura during treatment with methylprednisolone and cyclophosphamide (Cree *et al,* 2003). We have previously observed persistent Coxsackie B encephalitis resulting in severe encephalitis manifested by intractable seizures and coma (Berger *et al,* 2006). However, to the best of our knowledge, Coxsackie meningoencephalitis has not been previously reported with HIV/AIDS. Furthermore, we are unaware of any reports of coxsackievirus being demonstrated incidentally in brain tissue and did not detect it by real-time *in situ* PCR in the tissue of more than 50 control brains using the same technique. One study (Dix *et al,* 1994) of routinely performed CSF viral cultures in AIDS patients revealed that 11 (4.1%) of 269 samples were positive for enterovirus. These viruses were not further classified. Eight of these individuals were neurologically asymptomatic and CD4 counts were frequently in the normal range (Dix *et al,* 1994). No association between MS and enteroviruses has ever been established (Dessau *et al,* 1997; Kuusisto *et al,* 2005). Coxsackie B has been reported to cause aseptic meningitis, encephalitis, and flaccid paralysis (Ropka and Jubelt 2003). Persistent infection of the CNS has been reported in children with agammaglobulinemia (McKinney *et al,* 1987). This illness may be characterized by altered sensorium, weakness, hearing loss, seizures, ataxia, and paresthesiaes (McKinney *et al,* 1987). Enteroviruses like Coxsackie are not generally seen in association with HIV infection as humoral not cellular immune abnormalities predispose to their development. Consequently, coxsackievirus was unanticipated before autopsy and immunoglobulin studies were not obtained preterminally. We suggest that Coxsackie B leptomeningoencephalitis resulted in a relapsing-remitting neurological disorder that mimicked MS in our patient.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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This paper was first published online on iFirst on 13 May 2009.