INTRODUCTION

Acute transverse myelitis is a neurological syndrome resulting from inflammation of the spinal cord [1]. It is characterized by a variety of presentations depending on the level at which the spinal cord is involved, the location of the lesions, and the affected tracts. Signs and symptoms are commensurate with motor, sensory, or autonomic dysfunction, including paraparesis, flaccidity, spasticity, sensory impairment, bladder, bowel, and sexual dysfunction [2]. The clinical course may be monophasic or recurrent with variable remission rates depending on the underlying etiology [3]. While the exact trigger for this inflammatory process is yet to be identified, several conditions seem to be associated with the occurrence of transverse myelitis. Among the infectious etiologies, Mycoplasma pneumoniae, Borrelia burgdorferi, Treponema pallidum, and various viral pathogens have been implicated, including HIV, influenza, rubella, mumps, and all herpes viruses [4-8]. The diagnosis is suspected based on clinical signs and symptoms and is usually confirmed with MRI signal abnormality in the spinal cord, cerebrospinal fluid (CSF) pleocytosis, or both [9]. Transverse myelitis caused by herpes simplex virus-2 (HSV-2) is rare, and only a small number of cases have been reported in adults. Herein, we report a case of transverse myelitis due to HSV-2, with persistent viral replication in the CSF despite complete neurological recovery.

CASE REPORT

An 85-year-old man with an unremarkable medical history presented to the emergency unit with bilateral lower extremity weakness of five days duration. The patient was unable to stand from a sitting position without help but did not complain of any pain. He denied headaches, neck pain, visual disturbances, facial asymmetry, upper extremity weakness, or paresthesias. He had normal bowel and bladder control but reported urinary frequency. He did not report a recent febrile illness and his family verified normal cognitive and mental function. Upon review of systems, he described a history of a recurrent rash on the back and buttocks for the past 20 years, with a recent flare two weeks prior to presentation.
At the time of admission, physical examination revealed low-grade fever and stable vital signs. He had prominent grouped eroded lesions over the sacral area (back and buttocks). Neurological examination demonstrated 4/5 motor power in both lower extremities without any sensory deficit. Deep tendon reflexes were exaggerated with dorsal plantar responses bilaterally. The rest of the physical examination was unremarkable.

Pertinent laboratory findings following admission were as follows: white cell count 11,600 cells/mm³ with 93% neutrophils and a C-reactive protein of 8.2 mg/dl. CSF analysis revealed 80 white cells/mm³ (95% lymphocytes and 5% monocytes), 5 red cells/mm³, and a protein level of 0.55 g. Serum HIV-1 and 2 antibodies were negative and VDRL (venereal disease research laboratory) test for syphilis was nonreactive. In the CSF, HSV-1 and 2 IgM were negative whereas HSV-1 and 2 IgG diluted was positive and undiluted low positive. MRI of the brain showed two areas in the left frontal lobe representing infarcts likely venous in nature with the posterior one showing hemorrhagic transformation. MRI of the spine showed high T2 density foci at T8-T9 levels suggestive of transverse myelitis of possible post-infectious etiology (Figure 1).

On the basis of the spine MRI findings and the worsening clinical picture, the patient was started on acyclovir 10 mg/kg intravenously every 8 hours. HSV-2 myelitis was confirmed two days later via positive PCR in the CSF.

The patient’s condition improved gradually on antiviral therapy. Repeat CSF examination on day 4 of hospitalization showed a drop in the white cells to 10 cells/mm³, 88% of which were lymphocytes. Protein level in the CSF also decreased to 0.39 g. During his hospital stay, the patient continued to improve until he regained full power in his lower extremities; the skin lesions resolved completely leaving an area of hyperpigmentation. However, repeat PCR for HSV-2 in the CSF was still positive. After completing a 21-day course of intravenous treatment, he was discharged on oral valacyclovir to be continued for life as suppressive therapy.

HSV-2 PCR remained positive in the CSF until four months from the initial presentation despite full neurological recovery. A follow-up MRI of the dorsal spine confirmed resolution of the previously described changes at T8-T9 (Figure 2).

A year later, the patient returned with a new skin eruption at the same site and recurrent mild motor weakness. He admitted to having stopped valacyclovir two weeks earlier. He refused hospital admission and oral valacyclovir was resumed with subsequent improvement in his symptoms.
DISCUSSION

To our knowledge, there is a recent case report describing the occurrence of transverse myelitis in the setting of severe HSV-2 infection, and the trigger was influenza vaccine. However, lumbar puncture was not repeated to determine whether HSV viral shedding persisted or not [10].

We describe a patient who developed acute transverse myelitis following flare-up of a chronic HSV-2 infection. In our case, despite clinical improvement, there was evidence of continued viral replication for several months after treatment. The patient was discharged on life-long suppressive therapy with valacyclovir. The rationale behind this decision was to prevent reactivation of the virus; this is indeed what occurred when suppressive antiviral therapy was stopped.

An unexpected finding is that the HSV-1 and 2 IgM antibody test was negative. This could be a false negative result as the sensitivity of IgM antibodies in the CSF is only 75-85% [11].

Approximately 20-40% of cases of transverse myelitis are caused by viral infections with herpes viruses being the most frequent underlying pathogens. To our knowledge, the first case of herpes simplex myelitis was reported by Klastersky et al. in 1972 [12], in which HSV-1 was isolated from CSF. Since then many reports have been published describing patients with transverse myelitis associated with members of the Herpesviridae family.

A positive CSF PCR result indicates the presence of viral nucleic acid and is, in general, a marker of recent or ongoing active central nervous system viral infection by that particular pathogen, especially in an immunocompetent individual. What is of relevance in our present case is the prolonged time to CSF viral clearance after the initiation of antiviral treatment. While viral shedding in the CSF may persist for 2-4 weeks after the onset of clinical disease, this may be longer in immunocompromised patients. The first report to show prolonged detection of HSV in CSF was reported in 2012 by Ganzenmueller et al. Ganzenmueller reported the case of HSV radiculitis in a highly immunocompromised patient with hematologic malignancy where serial CSF viral quantitative studies still rendered positive results after 54 days. Marked clinical improvement was noted after three weeks of antiviral therapy despite the persistence of viral load in the CSF. The report highlighted the importance of further studies on HSV DNA kinetics in the CSF and their significance for an appropriate antiviral treatment.

While the present case also depicts an extended detection of HSV-2 in the CSF, it is unique in that it is, to our knowledge, the first report that describes this phenomenon in an immunocompetent patient. In the present case, restoration of muscle strength and control of urinary function occurred few days after the initiation of acyclovir while PCR remained positive for a period of four months. While the exact pathogenesis of HSV-2 persisting in the CSF is yet to be determined, several plausible hypotheses can explain this finding.

HYPOTHESIS 1 - PCR techniques allow for the in vitro synthesis of millions of copies of a specific gene segment, allowing the rapid detection of as few as 1 to 10 copies of target DNA from the original sample. PCR testing on CSF offers results with high sensitivity and specificity of 98 and 94% respectively. This is extremely helpful in early detection of infection and initiation of proper management. However, a major drawback of utilizing PCR is its inability to distinguish live from dead viral pathogens [13,14]. Thus the persistence of a viral load for an extended duration may be due to PCR's detection of dead viral DNA.

HYPOTHESIS 2 - There has been much controversy surrounding the pathophysiology of neurological complications associated with viral infections. While some researchers supported an immunological pathogenesis, others have identified direct viral invasion of neurons as the underlying etiology. The latter hypothesis is a plausible explanation for the persistence of HSV-2 DNA detected by PCR. Spinal cord invasion with HSV-2 followed by persistent subclinical viral shedding can account for the resolution of symptoms. In a study conducted by Phipps et al. on 377 patients with symptomatic HSV-2 infection, it was shown that while HSV-2 shedding decreased after the first episode, the level of shedding might persist at high levels for years following a primary infection or a recurrence [15]. No similar study has been conducted on CSF to address the issue of persistence of viral shedding.

HYPOTHESIS 3 - The results found on serial CSF analysis represent false positive results. Though highly unlikely, the HSV-2 DNA that was detected on PCR for an extended duration could be a result of skin contamination [16] from the area where the patient reported recurrent vesicular lesions. The introduction of newer real-time RT-PCR assays has offered several advantages, one of which is a lower risk of carry-over contamination compared to standard PCR assays. In the present case, CSF analysis was carried out with RT-PCR and the sampling was performed at a time where no skin lesions were visible. This does not completely rule out contamination but makes this rationalization as the underlying cause of prolonged detection highly unlikely.

We conclude that prolonged viral shedding in the CSF may occur in immunocompetent patients with herpes simplex myelitis. In the setting of adequate clinical improvement, repeated sampling of the CSF is not warranted and may not reflect actual viral activity.

REFERENCES