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CASE REPORT

A Case of Relapsing-Remitting Illness Due to Varicella Zoster Virus Vasculopathy in an Immunocompetent Adult

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Abstract

Varicella zoster virus (VZV) is an uncommon cause of meningitis in immunocompetent adults and has been implicated as the cause of vasculopathy, in literature. Here, we describe a case of aseptic meningitis which was followed by relapsing-remitting illness that was ultimately attributed to VZV-related vasculopathy. This case report emphasizes the importance of appropriate virologic testing in cases of aseptic meningitis and maintaining a high index of suspicion for VZV as a causative etiology even in immunocompetent subjects without typical herpes zoster infection.

Keywords: Varicella Zoster Virus Infection; Stroke; Aseptic Meningitis; Central Nervous System Vasculitis; Varicella Zoster Encephalitis.

Introduction

Meningitis with lymphocytic pleocytosis often poses a diagnostic challenge as the list of possible etiologies is long, and diagnosis requires correlation between clinical, laboratory, and imaging data. The etiology remains unclear in majority of the cases.[1] Varicella zoster virus (VZV) is rather a rare cause of aseptic meningitis and typically presents in association with preceding rash in immunocompromised individuals.[1,2] Here, we present a case of aseptic meningitis which was followed by recurrent episodes of neurological deficits that led to the identification of varicella zoster virus as the causative etiology, and complication in the form of vasculopathy was recognized.

Case Presentation

A 40-year-old previously healthy lady of Indian origin had recurrent neurological illness with repeated hospitalizations over a period of four months. The illness first started with headache, neck pain, nausea, vomiting, and photophobia. She was suspected to have meningitis and was evaluated. Her cerebrospinal fluid (CSF) showed lymphocytic pleocytosis and a mildly elevated protein level. The CSF was negative for Gram stain, fungal stain, cryptococcal antigen, acid-fast bacilli (AFB), bacterial culture, Mycobacterium tuberculosis (TB) polymerase chain reaction (PCR), TB culture, and Brucella antibodies. QuantiFERON-TB Gold test and Mantoux test were negative. Complete blood count, blood glucose, kidney function test, electrolytes, liver function test, thyroid function test, urine analysis, and erythrocyte sedimentation rate were normal. Chest x-ray was normal. Computerized tomography (CT) scan of the brain without contrast, magnetic resonance imaging (MRI) of the brain with contrast, MR angiogram, and MR venogram did not reveal any abnormality. She was empirically treated with broad-spectrum antibiotics including

ceftriaxone and dexamethasone. She improved over a period of one week.

After a month of asymptomatic period, she presented to this hospital with one-day history of slurring of speech, deviation of angle of mouth to the left, weakness in the right hand, and imbalance while walking. She had no headache, nausea, or vomiting. She had history of cough with scanty sputum over the last 3 weeks. On examination, she was alert and oriented, speech was mildly slurred, and gait was ataxic. There was no neck stiffness. Systemic examination was normal, and there was no skin rash. This time, her brain MRI with contrast showed multiple hyperintense foci in T2 and fluid-attenuated inversion recovery (FLAIR) in pons without enhancement, a small focus of increased signal in the left cerebellar hemisphere with enhancement, and small subcortical foci of increased signal in both frontal regions and left thalamus. The lesions in the pons showed restriction on diffusion-weighted imaging (Figure 1). The CSF analysis revealed lymphocytic pleocytosis. The results of her serial CSF analyses are summarized in Table 1. The CSF further showed positivity for VZV PCR. The PCR for herpes simplex virus 1 and 2, Epstein-Barr virus, human herpes virus 6, cytomegalovirus, and TB was negative. The CSF

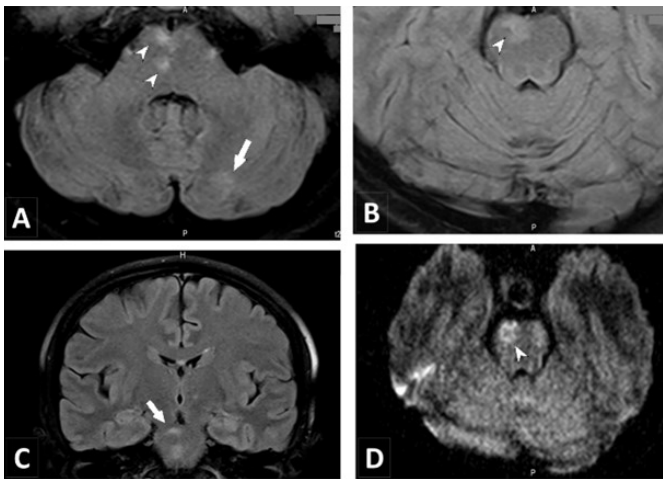

Figure 1: MRI images of the patient. (A) and (B) Hyperintense lesions in T2 FLAIR axial images at the level of pons (arrowheads) and subtle hyperintensity in the left cerebellum posteriorly (arrow); (C) Lesions in pons (arrow) on T2 FLAIR coronal section; (D) Diffusion restriction in the pontine lesion (arrowhead) on diffusion-weighted image.

Table 1: Summary of cerebrospinal fluid analysis results over the course of illness.

Duration from clinical onset	Glucose mg/dL	Protein mg/dL	Cell count cells/ cumm	Differential %	RBC cells/ cumm
Week 1	62.0	65.9	120	90% L, 10% M	20
Week 7	56.0	42.8	100	94% L, 6% M	50
Week 9	51.1	39.8	45	98% L, 2% M	50
Week 13	54.1	24.6	50	100% L	0
Week 15	68.9	16.7	7	100% L	0

L: Lymphocyte, M: Monocyte, RBC: Red blood cells

IgG index was elevated to 1.232 (normal range 0.3-0.7). The VZV antibody index in the CSF was 15 (normal range 0.6-1.5). The CSF anti-Hu, anti-Ri, and anti-Yo antibodies were negative. CSF was again negative for cryptococcal antigen and Brucella antibody. The CSF angiotensin-converting enzyme levels were not elevated. CSF cytology did not show any malignant cells. Serum was negative for antinuclear antibodies (ANA), anti-dsDNA, anti-SSA, anti-SSB, anti-Smith, anti-RNP, anti-Scl-70, anti-Jo1, p-ANCA (MPO), and c-ANCA (PR3). She tested negative for HIV and venereal disease research laboratory test (VDRL). Her blood counts, erythrocyte sedimentation rate, and C-reactive protein were normal. Her sputum examination showed positivity for chlamydia. Three serial AFB tests on sputum were negative. Her CT of thorax did not show any significant abnormality.

Following the diagnosis of VZV meningitis-associated vasculopathy, she was started on injection acyclovir 12 mg/kg intravenously thrice a day. Ceftriaxone injection was continued for the first week for chest infection on the recommendation of the pulmonologist. She improved neurologically over one week, and CSF analysis was repeated at the end of 10 days, which showed partial resolution and was negative for VZV PCR. As she had improved completely clinically, it was decided to stop acyclovir injection, and she was discharged on oral valacyclovir 1 g thrice a day for 1 week.

She was doing well on follow-up over the next three weeks and then one day, she had onset of dizziness,

imbalance while walking, vomiting, and shaking of visual images. On examination, she was alert, oriented, had horizontal jerk nystagmus beating to the right in all directions of gaze, was swaying to either side while walking, and tandem gait was impaired. There was no neck stiffness. In view of new neurological deficits, brain MRI was repeated which did not show any new lesions. CSF showed lymphocytic pleocytosis, however, was negative for VZV PCR. She was started on acyclovir and dexamethasone injections. This time, acyclovir was given for 14 days. Her symptoms improved significantly in the first week. The CSF analysis was repeated, which showed a normal picture and was negative for VZV PCR. At follow-up, she continued to be asymptomatic and was doing well.

Discussion

VZV is a double-stranded DNA virus which causes chickenpox as primary infection and then becomes dormant in the ganglia of nerves. The virus is known to reactivate and cause a number of neurological complications like herpes zoster, meningitis, encephalitis, myelitis, cranial neuropathy, and vasculopathy.[2] In the present case with initial presentation of aseptic meningitis, exhaustive testing for etiology was not done, and the virus remained undetected at that stage. The inability to reach an etiological diagnosis in case of aseptic meningitis has been well documented in the literature as the virus remains unidentified in up to 81% of the patients.[1]

The patient in our case study had two relapses over 3 months with focal neurological deficits. The vasculopathy following VZV infection has been shown to have a protracted course in an earlier series where time to virus identification from onset of neurological illness ranged from one day to two years (average 4.2 months).[3] In this series, even the onset of neurological symptoms following rash was delayed for an average of 4.1 months.[3] The patient presented in the current report never had a rash. The kind of pontine lesions that were seen have been described earlier in another case report as brainstem encephalitis.[4] In the absence of abnormality on vascular imaging and lack of histopathological evidence, the distinction between encephalitis and vasculitic infarcts may be arbitrary. The MR angiogram of this patient did not show any focal stenosis. In earlier reported cases, vessel imaging was able to pick up stenosis in only 70% cases. Possibly, small vessel involvement cannot be picked up on MR angiogram.[5]

The CSF VZV PCR in this patient was positive more than one month after the onset of meningitis, indicating that the virus may persist for long if specific treatment is not initiated. The VZV antibody index in the CSF was high as well and this is in fact a more sensitive evidence of VZV vasculopathy.[3] It has been postulated through histopathological evaluation that VZV enters the artery from adventitia, disrupts the intima, and ultimately promotes thrombotic occlusions.[6]

The 10-day course of intravenous acyclovir followed by oral valacyclovir for one week was not sufficient in this patient for normalization of CSF. Although the VZV PCR became negative, the lymphocytic pleocytosis continued. It was only after the second relapse that acyclovir injection along with dexamethasone injection for 14 days helped in achieving normal CSF counts. There is no information in the literature regarding the time taken for CSF to become normal. Also, there is no consensus on the optimal management of VZV meningitis and vasculopathy.

Conclusion

This report describes a case of VZV meningitis complicated by vasculopathy in an immunocompetent host who required multiple hospitalizations, repeated CSF analyses, and prolonged course of antiviral medications. A high index of suspicion coupled with appropriate use of diagnostic modality would be the way forward in identifying such cases. Timely recognition is important because of implications of therapeutic use of antiviral medications. With VZV being increasingly recognized as the cause of stroke in children and adults, newer diagnostic modalities like high-resolution MRI for vessel wall imaging and VZV microparticle detection in blood have been proposed.[7,8] However, further studies may be needed before they can be recommended.

Conflict of Interests

There is no conflict of interest.

Acknowledgments

None.

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