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Case Report Open Access

Neurological Sequale of Varicella Zoster Virus Infection

Shamaelah Javed[1*], Maheep Singh[2], Ramandeep Sahni[3], Stephen Marks[2], Michael Tenner[2], George Kleinman[2] and Ahluwalia Singh Brij[2]

[1]*Department of Neurocritical Care, Detroit Receiving Hospital, Wayne State University, USA*

[2]*Westchester Medical Center, USA*

[3]*Department of Neurology, New York Medical College, USA*

[*]**Corresponding author:** Shamaelah Javed, Department of Neurocritical Care, Detroit Receiving Hospital, Wayne State University, USA, Tel: 484-885-9816; E-mail: Shamaelah@gmail.com

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Abstract

Background: Varicella-zoster virus (VZV) meningoencephalitis is an uncommon complication in immunocompetent adults. Typically, most patients present with neurological symptoms within 7-10 days of onset of rash. Also neurological symptoms preceding the rash or in the absence of the rash are rare.

Methods: A 50 year-old female experienced urinary and bowel retention and numbness of heel for three days. She had a painful rash on her right thigh eight weeks earlier. MRI was normal. VZV PCR was positive in the CSF. Her neurological symptoms resolved with Acyclovir.

A 23 year-old woman experienced left lower extremity weakness and numbness of right leg and abdomen and urinary retention for one week. She had decreased pin prick in right leg up to T8 level. Serum Hepatitis B and Varicella Zoster virus antibodies were positive. MRI showed restricted diffusion and T2/FLAIR hyperintensity in the pons, mid brain and medial temporal lobe. She was treated with steroids and IVIG. After one month she developed fever, blurry vision and vesicular rash on left forearm. Skin biopsy was positive for Varicella zoster virus antibody. Retinal necrosis was found to be consistent with Varicella zoster virus infection. Patient improved neurologically on Valtrex 1 gm t.i.d.

An 84-year-old male had symptoms of severe radicular thoracic pain, urinary and bowel incontinence for one week. MRI of the thoracolumbar spine showed a Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation intradural, intramedullary enhancing lesion at the T7-T8 level with extensive edema. Autopsy revealed viral encephalomyelitis involving the medulla and multiple foci within the spinal cord with inflammation, necrosis, along with Cowdry viral inclusions consistent with Varicella-zoster virus.

Conclusion: The above mentioned cases high light atypical presentation of varicella zoster virus infection. The possibility of varicella zoster virus infection should be considered in patients presenting with unexplained myelopathy and restricted diffusion changes, mass lesion or unusual CNS symptoms.

Importance: Multiple neurologic complications may follow the reactivation of varicella-zoster virus (VZV), including herpes zoster, vasculopathies, myelitis, retinitis, and zoster sine herpete (pain without rash). Myelitis is one of the rarest neurological complications of VZV infection.

Observations: We report three cases of VZV myelitis; two of them were immunocompetent and in two cases, myelitis was associated with concomitant cerebral and brain stem strokes.

Conclusions and relevance: In immunocompetent patient VZV myelitis can manifest in the absence of a rash. Diffusion weighted images on MRI can be normal in the setting of acute myelitis due to VZV infection requiring CSF, VZV, PCR analysis to make prompt diagnosis and appropriate early treatment can lead to full recovery. Oral treatment for VZV rash does not preclude development of myelitis and may require intravenous antiviral medications to treat the infection subsequently. VZV infection can present as mass lesion of the spinal cord. Concomitant cerebral hemisphere and brain stem ischemic lesions and myelitis can occur due to VZV infection.

Case Report

Case 1

A 50 year-old woman presented in December 2012 with urinary and bowel retention and left heel numbness for three days. Eight weeks earlier she had painful vesicular eruption on right thigh for which she received oral antiviral treatment. MRI of the lumbosacral spine at outside hospital revealed degenerative disc disease. The patient was catheterized and a large volume of urine was obtained. Patient was referred to our hospital for further management. Neurologic

examination revealed decreased sensation in perineal and perianal areas and left heel with brisker reflexes in the lower extremities.

Complete blood cell count, liver enzymes, BUN, creatinine, C-reactive protein, erythrocyte sedimentation rate and urinalysis were normal. Anti-nuclear antibodies, anti-double stranded DNA, RPR, serum oligoclonal bands, Lyme titers were done to rule out infectious and inflammatory causes which were also negative. Cranial MRI examination revealed nonspecific T2 white matter changes. MRI of spinal axis with and without contrast revealed only minor degenerative disc changes at C5-C6 and C6-C7. CSF fluid analysis revealed WBC 247/cu mm, lymphocytes 95%, Proteins 83 mg/dl, Glucose 43 mg/dl, IGG 8.60, IGM 0.60 (N<0.5). CSF VZV PCR was positive and the patient was treated with acyclovir IV 800 mg t.i.d. and solumedrol 500 mg q. 6h. By Day 3 patient noticed improvement in the left heel numbness and regained sphincter function. On a follow up visit at two weeks and two months the patient remained neurologically stable.

Case 2

A 23 year-old woman presented in February 2013 complaining of weakness of left lower extremity and numbness of right lower extremity extending up to mid thoracic region of three days duration. She was diagnosed to have Systemic Lupus Erythmatosus three months earlier and received steroids and azathioprine. She developed urinary retention and inability to walk. MRI of the brain at an outside hospital revealed a right pontine infarct.

Neurologic examination at our hospital revealed weakness of right genioglossus and of the entire left lower extremity with decreased sensation on her right side below the T8 level. She was continued on Solumedrol 250 mg IV q. 6h and azathioprine 100 mg daily.

Laboratory results revealed blood white cell count of 11.0/cumm with neutrophilia, erythrocyte sedimentation rate of 60 mm/hr, normal liver enzymes, BUN, creatinine and urinalysis. Serum VZV IgM and IgG antibodies, antinuclear and anti dsDNA antibodies were positive. The rest of the autoimmune panel and hypercoagulable tests were normal. HIV was negative.

MRI revealed multiple foci of abnormal signal in the left and right frontal lobe, right paramedian pons, dorsal midbrain and right ventrolateral medulla. MRI of the cervical and thoracic spine revealed 4 discrete foci of abnormal T2/STIR hyperintensites in the thoracic spinal cord with the largest focus in the left lateral cord at the T2 level. Additional tiny foci of signal abnormality were identified at the T5 and T8 vertebral body levels and at the T11-T12 disc level.

CSF fluid analysis revealed WBC 39 cu/mm, lymphocytes 93%, PMN 2%, RBC 20 cu/mm, glucose 65 mg/dl, proteins 41 mg/dl and positive VZV, EBV, DNA and PCR. She was treated with IV solumedrol 250 mg q. 6h transitioned to oral prednisone, intravenous Valacyclovir 800 mg t.i.d switched to oral Valtrex, Plaquanil, Fluconazole for antifungal prophylaxis as patient was immunocompromised, IV Ceftriaxone and Meprone for PCP prophylaxis. CSF studies after four weeks revealed WBC 41 cc/mm, lymphocytes 62%, PMN 18%, RBC's 18 cc/mm, glucose 74 mg/dl and proteins 48 mg/dl and positive VZV PCR. After six weeks of onset of neurological symptoms patient developed high grade fever and vesicular rash on left forearm and blurry vision. Repeat CSF fluid analysis at six weeks revealed WBC 55 cu/mm, Lymphocytes 92%, RBC's 2000 cu/mm, glucose 37 mg/dl and proteins 175 mg/dl and continued VZV PCR positivity.

Skin lesion was positive for VZV by monoclonal antibody direct stain. Patient received Intravitreous Gancyclovir for retinal necrosis. Brain MRI Brain revealed Interval development of restricted diffusion encompassing the left basal ganglia, left precentral gyrus, and left cerebellar hemisphere. New foci and an increase in size of the restricted diffusion in the right occipital and posterior temporal lobe were noted without evidence of hemorrhagic conversion. MRI spinal cord was unchanged with four foci of abnormal T2/FLAIR hyperintensity within the thoracic cord.

Neurological examination remained unchanged. In view of presumed acute ischemic changes on MRI the patient received IVIG as per rheumatology for possible cerebral lupus. She was also started on heparin for a few days. She developed autoimmune hemolytic anemia due to the IVIG, confirmed by Direct Coomb's test. She received oral prednisone for autoimmune hemolytic anemia. Heparin was discontinued in light of normal transthoracic echocardiogram and after the possibility of Leibman Sach's endocarditis was ruled out. She was improving neurologically and was sent to rehabilitation.

On April 6th 2013, she was found to have right upper extremity weakness and intermittent episodes of aphasia. Neurological exam revealed weakness in the right lower extremity and decreased sensation on the right side below T6 in addition to the previously noted left lower extremity weakness.

MRI brain revealed a 4 cm intraparenchymal hemorrhage in the paramedian inferior left frontal lobe with associated mass effect and mild subfalcine herniation at the site of previous subacute ischemic infarct. Interval development of a few new small foci of acute/early subacute ischemic infarct in the left middle frontal gyrus and left precentral gyrus were noted.

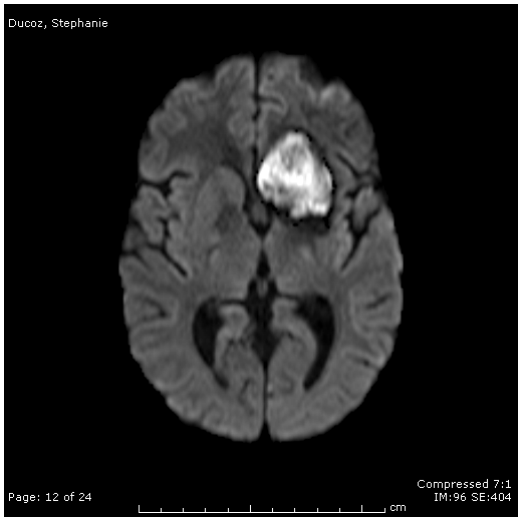

Figure 1: Diffusion weighted sequence showing restricted diffusion in left basal ganglia.

Repeat CSF analysis revealed WBC 33 cu/mm, RBC 1 cu/mm, Lymphocytes 94%, PMN 1%, Glucose 41 mg/dl, Proteins 101 mg/dl. VZV, PCR was negative in CSF and serum. Repeat hypercoagulable and vasculitis work up including Factor V leiden, homocysteine levels, protein c and s, Prothrombin gene g20210 a, Anti–SS-A/RO, Anti SS-

B/La, Anti –RNp, Anti Jo-1, Anti-cardiolipin abs were unremarkable except for positive ANA and anti- dsDNA antibodies.

The patient improved neurologically with resoluation if aphasia and improvement in right upper extremity weakness. Repeat MRI brain, Spine and MRA head and neck showed stability of the lesions with no further progression. The patient was discharged for acute rehabilitation on Valtrex 1 gm t.i.d., Plaquenil 200 mg b.i.d., steroid taper and Mepron 750 mg q. 6h. On follow up she had interval resolution of the neurological deficits except flattening of the right nasolabial fold and slight hyperesthesia of the left shoulder (Figure 1).

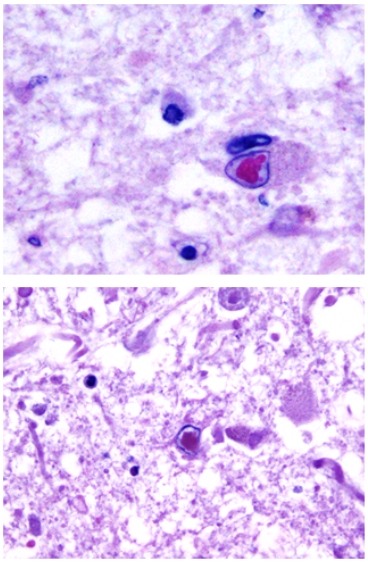

Figure 2: Cowdry type A inclusion bodies ON Autopsy specimen staining.

Case 3

An 83 year old man presented to ER with weakness and difficulty standing. Seventeen days earlier he had fallen down stairs without any significant trauma. He had past medical history of treated recurrent bladder cancer with intravesicular chemotherapy, hyperlipidemia and paroxysmal atrial fibrillation. Neurologic examination revealed a sensory deficit bilaterally below T8 level. MRI of the spinal cord showed abnormal signal at T5-T10 spinal cord suggesting a "mass" lesion with enhancing lesions at multiple thoracolumbar levels. CT of the chest, abdomen, and pelvis showed no evidence of metastatic disease (Figure 2).

Subsequently, he underwent T6-T9 laminectomy. Biopsy of a spinal cord lesion at T7-8 level showed neural parenchyma with inflammatory cells and gliosis. Left lower extremity weakness progressed to paraplegia. Repeat MRI of the thoracic and lumbosacral spine showed signal changes at the T2 and T3 levels. MRI of the brain showed restricted diffusion within the left medulla with mass effect and expansion of the left olivary eminence and a small amount of extension across the midline consistent with acute infarct. CSF was analyzed to rule out any infectious causes by negative CSF cultures. He received IV steroids with no improvement (Figure 3).

Repeat MRI showed evolution of infarction medulla. MRI of spinal cord showed multiple foci of intramedullary enhancement and restricted diffusion from C4 to T7 levels consistent with a large cord infarct. The patient started developing ileus and intestinal obstruction along with consistent fevers. He started deteriorating neurologically. His GCS never improved and remained 3 T. After discussion with family he was placed on comfort care only.

Autopsy revealed viral encephalomyelitis of the medulla. Spinal cord showed multiple foci of inflammation, necrosis, demyelination, gliosis, focal necrosis and thrombosis of small blood vessels, which contributed an element of ischemic injury and inflammation. Several Cowdry viral inclusions were identified in neural cells in spinal cord. Immunostaining was positive for VZV but negative for CMV/HSV (Figure 4).

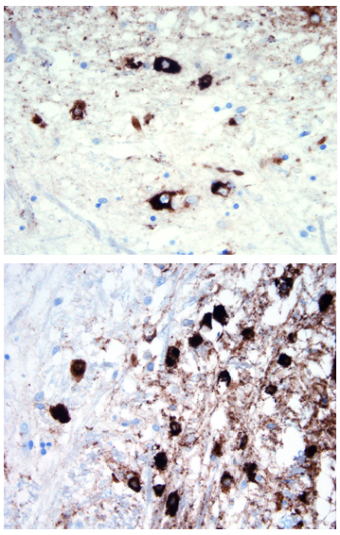

Figure 3: Immunostaining for VZV on autopsy specimen.

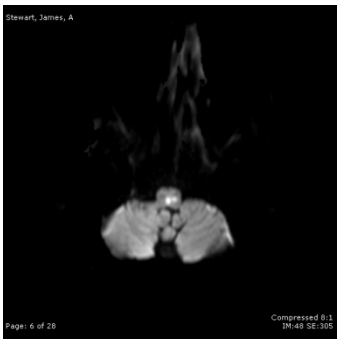

Figure 4: Diffusion weighted sequence showing restricted diffusion in brain stem and left cerebellum.

Discussion

The incidence of Varicella Zoster infection is increasing in the United States. One million new episodes of Zoster occur in the United States yearly with a lifetime risk of 30%. The percentage of zoster is 80% in patients 50 years or older. In Olmsted county, Minnesota, over 5 years from 1996-1997 to 2000-2001, zoster incidence increased from

3.2 to 4.1 per 1000 person in years, an increase of 28%, unexplained by age or immunological status [1].

Varicella zoster virus (VZV) primary infection causes chickenpox, which later subsequently becomes latent in cranial nerve, dorsal root and autonomic ganglia [2]. With advancing age or immunosuppression, cell-mediated immunity to VZV declines and the virus reactivates to causes pain and rash in a dermatomal distribution (Zoster). Zoster can be followed by postherpetic neuralgia, cranial nerve palsies, vasculopathy, multiple aneurysms [3], subarachnoid hemorrhage, carotid dissection, meningoencephalitis, ocular involvement and myelitis. Typical VZV infection causes vasculopathy involving large and small arteries causing ischemic lesions in the grey white matter junction.

Simultaneous involvement of brain, spinal cord and meninges in response to VZV reactivation is exceptional in an immunocompetent patient [4-6]. VZV encephalomyelitis can occur in the absence of a rash [7,8].

Based on retrograde axonal transport in studies in felines, Saito et al. [9] suggested a possible pathway of spread of VZV from dorsal root ganglia to posterior cerebral arteries and from trigeminal ganglia to anterior cerebral arteries. Devinsky et al. [10] reported VZV myelitis showing combination of vasculitis, necrosis and demyelination of spinal cord and suggested axoplasmic spread peripherally and centrally due to cell to cell contact.

Myelitis is one of the rarest complications of VZV infection [11-14] and usually develops in immunocompromised patients. The incidence varies from 0% to 0.8% in general population or immunocompromised patients respectively. Devinsky et al. [10] reported 13 patients with VZV myelitis. All were immunocompromised and seven of them had confirmed pathological diagnosis on postmortem examination showing demyelination, necrosis and vasculitis. In four patients VZV vasculitis was associated with leptomeningitis and hemorrhagic necrosis. There was no mention of cerebral cortex involvement.

We present three cases of VZV related myelitis, two of which were immunocompetent. To the best of our knowledge only two cases of VZV encephalomyelitis in immunocompetent patients have been reported previously [15,16].

In cases of abrupt onset of myelopathy Orm et al. [17] emphasized the use of DWI MRI along with virological analysis of CSF to definitely establish diagnosis of VZV infection. Our first patient had acute onset myelitis but normal DWI MRI. Only later CSF fluid analysis confirmed diagnosis of VZV infection. This case emphasizes that in acute onset myelitis where DWI MRI is normal, CSF analysis for VZV infection should be done to establish a correct diagnosis, as this is an eminently treatable condition if diagnosed early.

Gonzalez-Otarula et al. [18] reported a case of an immunocompetent patient with atypical Ramsay-Hunt syndrome sine herpete associated with acute brainstem stroke suggesting transaxonal spread of VZV from geniculate ganglion to brainstem and posterior circulation. The association between brainstem strokes and Zoster oticus has been described previously [19,20]. In our second case strokes in the anterior basal ganglia and posterior circulation(cerebellar) cannot be explained on the basis of tranaxonal spread from myelitis alone thus suggesting a more widespread VZV vasculopathy independent of transaxonal spread.

Our third patient, an immunocompetent person, with no history of rash but showed clinical and radiographical features of varicella zoster encephalomyelitis confirmed at autopsy. This case clinically presented as a "mass" lesion of the spine, an unusual presentation of VZV myelitis. Biopsy of the lesion showed only hypercellularity but on autopsy cowdry inclusion bodies and positive immunostaining for VZV in the spinal cord were present consistent with chronic active VZV induced ganglionitis [21].

Conclusions

VZV Myelitis can occur in immunocompetent patients (cases 1 and 3). DWI MRI imaging can be normal in the setting of VZV myelitis. CSF- PCR analysis may lead to diagnosis and proper treatment (case 1). Oral antiviral treatment of rash does not prevent subsequent VZV myelitis (Case 1). VZV Myelitis can present mimicking a "mass" lesion (case 3). Concomitant cerebral hemisphere and brain stem ischemic lesions and myelitis can occur due to VZV infection can occur (cases 2 and 3). Devastating encephalomyelitis can occur in the absence of rash especially in an elderly immunocompetent (Case 3).

Conflict of Interest

Dr. Shamaelah Javed, Dr. Maheep Birdi, Dr. Ramandeep Sahni, Dr. Stephen Marks, Dr. Michael Tenner, Dr. George Kleinman, Dr. Brij. S. Ahluwalia declares that they have no conflict of interest.

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