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Indolent varicella encephalitis with vasculopathy in an immunocompromised patient

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Abstract

A 68-year-old female with B-cell non-Hodgkin's lymphoma presented to us with sequential blindness followed by hemiparesis. Four months earlier, the patient had developed chicken pox that was treated with intravenous acyclovir. An MRI brain showed multiple cerebral infarcts and beaded appearance of her intracranial vasculature. PET-CT showed hypermetabolism in the right frontal lobe and pons suggestive of encephalitis. Cerebral spinal fluid examination showed 15 cells and varicella zoster vasculopathy (VZVV) polymerase chain reaction was positive. A final diagnosis of indolent VZVV vasculopathy and encephalitis in an immunocompromised individual was made. This case highlights the slow and indolent progression of varicella central nervous system involvement.

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Introduction

Varicella zoster vasculopathy (VZVV) is classically described in primary varicella infection or zoster reactivation when there is a temporal association with a stroke. VZVV was thought to be more common in ophthalmic zoster than in other dermatomes. However, both intracranial and extracranial arteries are now known to be associated with VZVV. It is unusual to have a varicella encephalitis coexisting with VZVV.[1] This report presents an unusual case of VZVV coexisting with varicella encephalitis in an immunocompromised female.

Case presentation

A 68-year-old Omani female presented with a history of altered sensorium of 4 days duration. In 2017 she developed a progressively increasing swelling in her right shin and weight loss of 20 kg. MRI of the right leg showed a destructive lesion with extraosseous tabulated soft tissue component around the tibial condyles. The proximal third of the lesion showed a pathological fracture. There was an intraosseous collection adjacent to the fracture (haematoma 23 × 3.3 cm). There was a displacement of the neurovascular bundle in the popliteal fossa. In August 2018, bone biopsies showed fragmented bone and sheets of medium-sized atypical lymphoid cells with marked necrosis and apoptosis. The atypical cells were CD20 diffusely positive and suggestive of B-cell non-Hodgkin's lymphoma. Further characterisation was not performed.

A whole body PET-CT showed hypermetabolic lymphadenopathy above and below the diaphragm, as well as bilateral lung nodules, small bowel lesions, right ovarian lesion, and right tibial and L2 bone lesions. CT spine showed compression fractures of T6 and L2 vertebrae associated with paravertebral soft tissue enhancement around L2 vertebra, as well as intraspinal extension. Chemotherapy (bendamustine) was started in November 2018; five doses were completed by March 2019. The patient used a walker until 6 months previously, when she was advised to use a wheelchair.

A repeat PET-CT 4 months later showed no evidence of lymphoma. One month after that, the patient developed chicken pox with generalised skin lesions. She was hospitalised and treated with 17 days of intravenous acyclovir until the rash resolved. Six weeks ago, the patient developed sudden onset of blindness of the right eye followed 1 week later by the left eye. At 1 week prior to admission, she developed right-sided weakness, dysarthria and recent memory loss.

On examination, she had apraxia of eyelid opening, dysarthria and right hemiparesis of grade 2/5. There was no light perception in either eye, fundoscopic examination showed bilateral optic atrophy and both plantar reflexes were extensor. MRI on day 2 after admission showed multiple acute infarcts scattered among the bilateral gangliocapsular region, left thalamus, left hippocampus, right corona radiata, right parietal cortex and left dorsal midbrain. New infarcts were noted in the right temporoparietal lobes,

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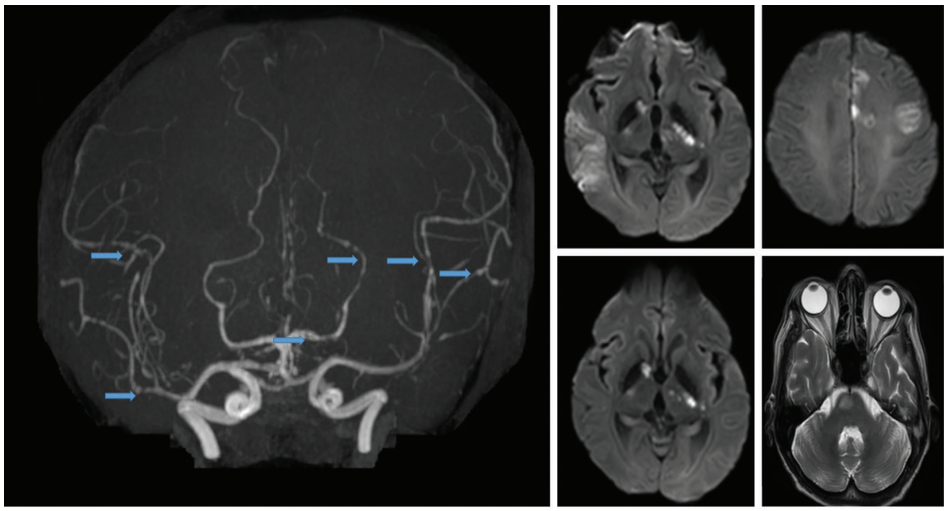

Figure 1 MR angiography and MRI images. Left panel shows an intracranial MR angiography with blue arrows depicting areas of stenosis. Right panels (diffusion-weighted MRI) show cortical and basal ganglia infarcts. The bottom right image is a T2-weighted MRI image showing a bulky right pontine hyperintensity

left parasagittal frontal cortex, left frontal lobe and genu of corpus callosum on the right side. There was a T2 hyperintensity without diffusion restriction involving the right cerebral peduncle, right central pons and medulla with the right pons appearing bulky. There were no contrast-enhancing lesions. MR angiography showed focal stenosis with beaded appearance bilaterally in the proximal and distal branches of the anterior cerebral artery, posterior cerebral artery, middle cerebral artery and supraclinoid left internal carotid artery (string of beads appearance) (Figure 1). Neck vessels were normal. The initial differential diagnoses were lymphomatous meningitis with vasculopathy or a secondary central nervous system (CNS) vasculitis. Initial cerebral spinal fluid (CSF) exam showed 25 cells, all lymphocytes with normal sugar and protein of 75 mg%. Flow cytometry was negative for lymphoma.

A new PET-CT showed fluorodeoxyglucose (FDG) avid lesions in the right frontal region involving the precentral gyrus and the right pons suggestive of encephalitis (Figure 2). No systemic evidence of lymphoma was found. The right tibia lesion was non-FDG avid. A repeat CSF exam showed 15 cells with normal sugar and high protein. An encephalitis viral panel (XCyton Diagnostics, India) was positive for varicella zoster (polymerase chain reaction).

With a diagnosis of ongoing VZVV and encephalitis the patient was restarted on acyclovir 10 mg/kg/day every 8 hours along with intravenous immunoglobulin 2 g/kg. The patient started showing some clinical improvement after 8 days of therapy and her hemiparesis improved to 5/5. On day 21, however, she developed aspiration pneumonia and was transferred to the intensive care unit. Her total white blood count dropped from 4,000 cells/mm^3 to <250 cells/mm^3 and on day 22 she went into multiorgan dysfunction and succumbed to her illness on day 23.

Discussion

VZVV was initially thought to be a noninfectious granulomatous CNS angiitis.[2] Subsequently, active viral infection of arteries was demonstrated in postmortem samples in >60% of cases.[3] Therefore, the treatment paradigm has been changed to manage virulent viral arteritis.

VZVV is known to affect intracranial or extracranial arteries, although the former is more common. Intracranial VZVV presents with cerebrovascular events, including transient ischemic attacks, ischemic or haemorrhagic strokes, aneurysmal subarachnoid haemorrhage, carotid dissection or prolonged headaches. Spinal cord infarction occurs

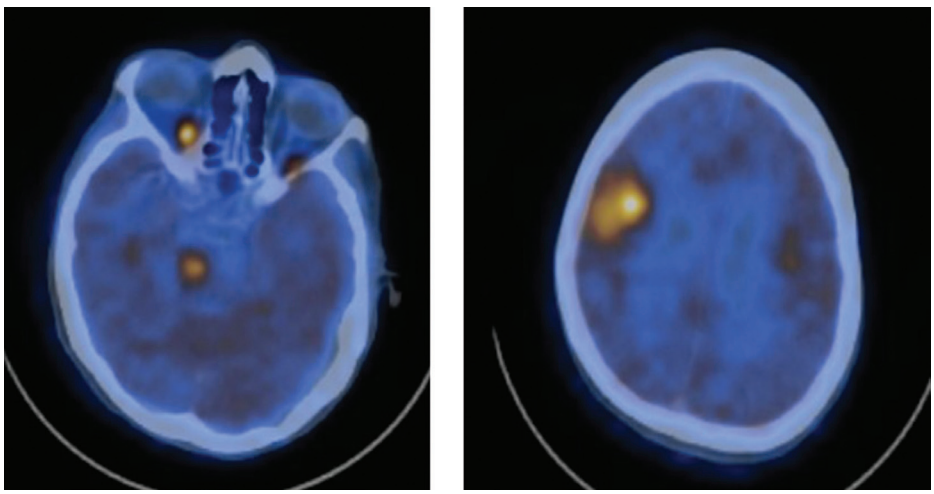

Figure 2 PET-CT images showing hypermetabolism in the right pons and right frontal region

when the radicular arteries are involved.[4] VZVV can involve arteries of any calibre. Unifocal arteries are seen after trigeminal zoster in elderly immunocompetent patients and involve the large arteries of the anterior or posterior circulation. Multifocal vasculopathy affecting both large and small arteries is more common in immunocompromised individuals.[5] Small vessel arteritis is exemplified by the occurrence of central retinal artery occlusion, posterior ciliary artery occlusion or retinal vasculitis with monocular vision loss in some cases.[5,6]

VZVV is a difficult diagnosis owing to the long delay between primary infection and onset of cerebrovascular events (ranging from 1 week to 2 years; mean 4 months), the occurrence of VZVV without an overt rash (zoster sine herpete) in 40% or normal CSF studies in 30% of cases. Moreover, clinicians may test for varicella zoster virus (VZV) DNA instead of VZV CSF IgG. Owing to the long latency of infection, the sensitivity of VZV DNA is only 30%, compared to VZV CSF IgG (93%). CSF shows pleocytosis in 67% and brain MRI shows multifocal lesions predominantly at grey–white matter junctions, some of which show haemorrhagic transformation due to blood–brain barrier disruption.[7] MR angiography or digital subtraction angiography are abnormal in around 70%, showing large or small artery stenosis or occlusion. Empirical treatment with acyclovir with or without steroids stabilises or cures only around 60% of patients with VZVV, possibly owing to the protracted course and late diagnosis. Treatment is mostly empirical owing to a lack of randomised controlled trials, the duration of treatment is variable and depends on the clinician's discretion and clinical response. Persistent VZVV after prolonged acyclovir treatment may require oral valciclovir for 1–2 months, but the outcome worsens with time.[3]

When VZVV is present, concurrent encephalitis is unusual and thought to be due to the VZVV itself. No reports have conclusively demonstrated any imaging changes of encephalitis in these cases. Our patient had VZVV and a coexistent encephalitis that was demonstrated by both MRI (nonenhancing lesion in the pons) as well as PET-CT (hypermetabolic lesions in the pons and right frontal region). We could not disprove the fact that vasculopathy was the primary cause of encephalitic changes owing to the lack of biopsy specimens. However, the pontine lesion did not show any diffusion restriction suggestive of ischemia and the frontal lesion also was not evident on MRI, thus making the PET-CT changes more likely to be encephalitic than otherwise.

Conclusion

VZVV is an important and treatable cause of a multifocal vasculopathy. Diagnostic testing should include both VZV DNA as well as CSF VZV IgG as the latter is much more sensitive. The primary pathology is due to a low-grade persistent viral arteritis. VZVV encephalitis could coexist rarely and may require PET-CT for diagnosis. Treatment is largely empirical and comprises prolonged courses of acyclovir. Immunosuppression is a risk factor for an indolent and progressive VZVV and encephalitis. Ongoing VZV infection should be suspected even when there is delayed neurological deterioration or multifocal cerebrovascular infarctions after a primary VZV infection or herpes zoster.

Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient/guardian for publication of this paper, including accompanying images.

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