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(CASE REPORT)

A Case Report on *Varicella zoster* Encephalitis Vasculopathy

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Abstract

Varicella zoster virus (VZV) encephalopathy is a rare but serious complication of viral reactivation, particularly in immunocompromised individuals. We report the case of an 83- year-old female with a background of autoimmune hemolytic anemia and high-grade B-cell non-Hodgkin lymphoma, previously treated with immunotherapy and chemotherapy and was in complete remission who presented after 1 year with fever, altered mental status, and a generalized vesicular rash. MRI brain revealed T2/FLAIR parieto-occipital hyperintensities and multifocal infarcts suggestive of vasculopathy/acute infarct. Cerebrospinal fluid multiplex PCR confirmed the presence of VZV. The patient had profound hypogammaglobulinemia, and was treated with intravenous immunoglobulin. Despite best supportive management, her neurological condition rapidly deteriorated. This case underscores the importance of maintaining a high index of suspicion for VZV encephalopathy in elderly, immunocompromised patients presenting with encephalopathy and rash. Early CSF analysis and neuroimaging are essential for diagnosis, and timely diagnosis and aggressive management may influence the outcomes in such high-risk populations.

Keywords: Varicella Zoster Virus; Encephalitis; Vasculopathy; Non- Hodgkin Lymphoma**;** Immunocompromised patients**;** Central nervous system

1. Introduction

Varicella-Zoster Virus (VZV), a neurotropic human alpha-herpesvirus,which is the primary causative agent varicella (chickenpox). Following primary infection, the virus establishes latency in cranial nerve, dorsal root, and autonomic ganglia. Reactivation of latent VZV, often triggered by immunosuppression or advanced age, results in herpes zoster (shingles), which may be associated with a range of complications. These complications, particularly those involving the central nervous system, tend to be more severe and frequent in immunocompromised individuals."The most common and significant complication of VZV reactivation is post herpetic neuralgia, a condition whose cause is currently unknown and for which effective treatments are generally lacking [1]. It is recognized as a frequent cause of central nervous system (CNS) diseases, presenting with a broad range of symptoms. The most commonly studied CNS complications include encephalitis, which can occur with both chickenpox (varicella) and shingles (herpes zoster), and cerebellitis, predominantly seen in children with chickenpox. Other ways VZV can affect the CNS haven't been as thoroughly researched [2]. The World Health Organization reports that encephalitis is a rare complication of varicella-zoster virus, occurring in approximately 1 out of every 33,000 to 50,000 cases. Furthermore, it tends to have a worse outcome than other complications of VZV that affect areas beyond the skin[3].

Immunocompromised adults infected with varicella–zoster virus (VZV) face a substantially increased risk of developing encephalitis, a severe central nervous system (CNS) complication. While VZV is classically recognized for its cutaneous manifestations, it can disseminate to involve multiple organs, including the CNS. VZV encephalitis may present with

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non-specific neurological symptoms such as altered mental status, confusion, vomiting, and seizures. In elderly patients, these manifestations may be particularly challenging to localize or attribute specifically to CNS infection due to overlapping comorbidities and atypical presentations.

The prognosis of VZV encephalitis is variable but can be grave. Reported mortality rates approach 15% in immunocompetent individuals and may reach nearly 100% in untreated immunosuppressed patients, particularly when there is concurrent hepatic or pulmonary involvement. Cerebrospinal fluid (CSF) analysis in VZV encephalitis often reveals lymphocytic pleocytosis and elevated protein concentration, as noted in the present case.

Polymerase chain reaction (PCR) detection of VZV DNA in CSF remains the most sensitive and specific diagnostic modality for confirming VZV encephalitis. While the detection of intrathecal anti-VZV antibodies can support the diagnosis, antibody testing alone is insufficient to establish the presence of VZV-related neurological disease. Thus, timely molecular confirmation via CSF PCR is critical to initiate appropriate antiviral therapy and improve patient outcomes, especially in high-risk immunocompromised populations [5].

2. Case report

An 83-year-old female with a known history of autoimmune hemolytic anemia and high-grade B-cell Non-Hodgkin lymphoma presented with acute onset of rapidly progressive neurological decline over 4 days. She had been experiencing reduced appetite, malaise,abdominal discomfort followed by fever and a vesicular rashes since 2 days.

The rashes were reddish,raised, vesicular with central dusky appearance some of them crusted in varying stages of evolution and were predominantly distributed over the face , trunk and proximal upper extremities than lower limbs.

She had a history of long standing Autoimmune Hemlytic anemia and was conservatively managed elsewhere. Two years later, she developed recurrent symptomatic anemia (Hb 4.8 g/dL)and B symptoms including significant weight loss and night sweats. Bone marrow biopsy revealed markedly hypercellular marrow with atypical lymphoid infiltrates.Staging CT was done prior to treatment and multiple supra and infradiaphragmatic lymphadenopathy was noted. Bioppsy of the involved node was deferred in view of the advanced age and the patient preferences and flowcytometry of the bone marrow revealed the presence of monoclonal B cells. Immunohistochemistry confirmed the presence of High-grade B-cell non-Hodgkin lymphoma positive for CD 20 and BCl2 infiltrating the marrow with a proliferation index (Ki-67) exceeding 80% , Stage 4 disease.

She was treated with 6 cycles of rituximab-based therapy. An interim assessment after 4 cycles showed significant disease remission and End of treatment assessment showed complete response to Deauville 1 score on PET CT. She was on irregular follow up eversince.

She was brought back to the hospital 9 months later with a short history of fever, progressive worsening of consciousness and development of generalized vesicular rashes over the body. On examination, she was febrile and unresponsive (GCS-E2V1M3), with positive neural tension tests. A dermatological evaluation considered differentials including varicella zoster, Kaposi varicelliform eruption, and eczema herpeticum.

Laboratory investigations revealed leukopenia (TC 1,800/µL), thrombocytopenia (Plt 87,000/µL), and Hb 11.1 g/dL. A single dose of filgrastim (G-CSF-300 mcg) was administered for neutropenia.

A CSF Analysis was done which showed raised CSF protein (101.7 mg/dl)with borderline low CSF sugars with lymphocytic pleocytocytosis and negative reports on ADA and Gram Stain.

Magnetic resonance imaging (MRI) of the brain showed diffuse gyral thickening and T2/FLAIR hyperintensities in the bilateral parieto-occipital lobes, with associated diffusion

restriction but no post-contrast enhancement, suggestive of inflammation/ vasculopathy seen in viral encephalitis or acute infarcts. Multiple acute lacunar infarcts were also seen in the ganglio-capsular regions, frontoparietal white matter, and cerebellar hemispheres. Additional findings included age related atrophy and chronic small vessel ischemic changes.

Cerebrospinal fluid (CSF) analysis was also tested by multiplex PCR testing (BioFire panel). The panel was tested positive for Varicella Zoster Virus, confirming the diagnosis of VZV encephalopathy with associated Vasculopathy in the background of characteristic radiological findings.

Treatment was initiated with IV Acyclovir along with other supportive measures. Given the patient's history of lymphoma and immunosuppressive therapy, further evaluation revealed hypogammaglobulinemia and she was treated with intravenous immunoglobulin (IVIG) at replacement doses. Despite initiation of supportive therapy including oxygen supplementation and intravenous fluids, her neurological condition worsened, with unresponsiveness to pain and gasping respiration. Pupils were sluggishly reactive. After multidisciplinary consultation and family discussion, in view of the poor prognosis and advanced disease status, the decision was made to proceed with best supportive care.She rapidly succumbed on Day 3 of hospitalization.

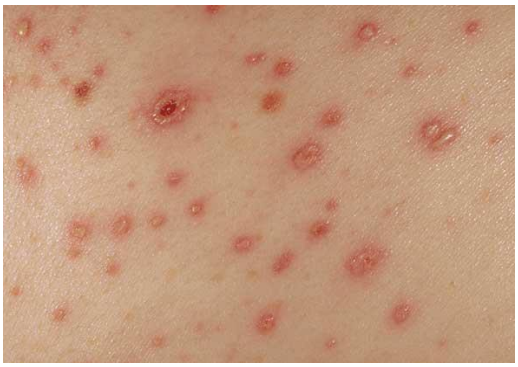

Figure 1 Image showing varicella associated Skin lesions

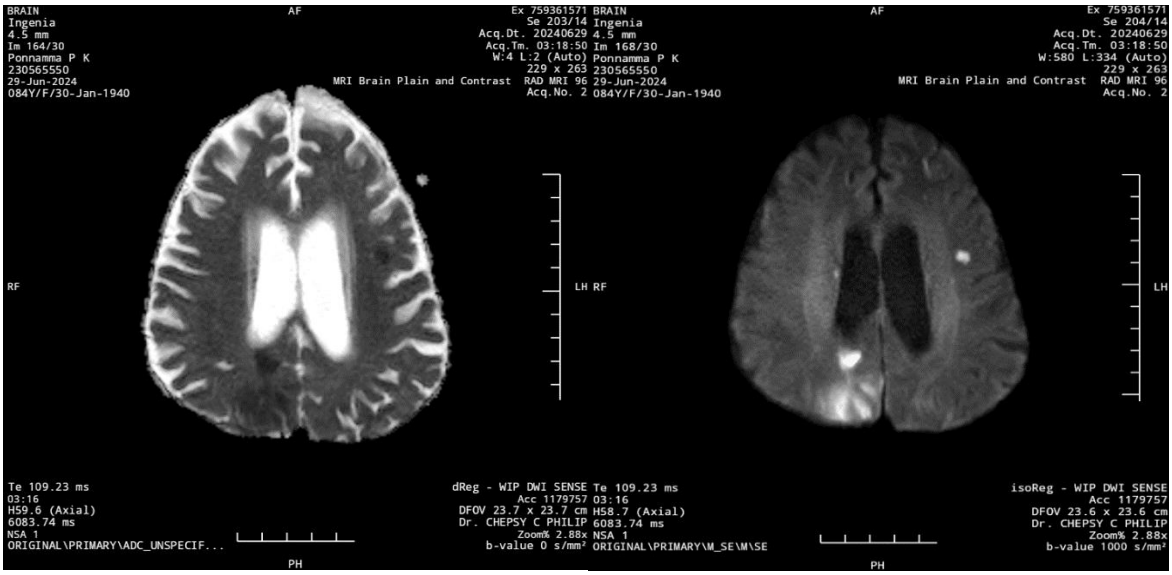

Figure 2 ADC and DWMRI showing Multiple Foci of Diffusion restriction in Right Parietooccipital Lobe , Left Frontoparietal Lobe

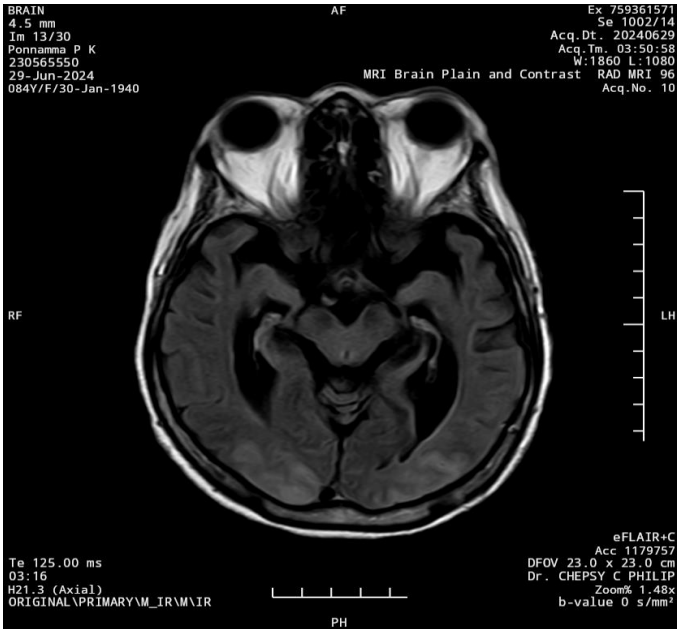

Figure 3 FLAIR Hyperintensities in bilateral Occipital Lobes

MRI of the brain revealed diffuse gyral thickening with T2-weighted and FLAIR hyperintensities involving the bilateral parieto-occipital lobes, accompanied by diffusion restriction on DWI sequences, suggestive of acute cortical involvement consistent with encephalitic changes. Additionally, multiple small, discrete, and confluent foci of diffusion restriction were noted in the bilateral fronto-parietal white matter, ganglio-capsular regions, and cerebellar hemispheres, with corresponding FLAIR hyperintensities, indicative of likely acute lacunar infarcts. Given these imaging findings, in conjunction with a positive CSF PCR for Varicella zoster virus, the overall picture is suggestive of Varicella encephalopathy/vasculopathy with associated multifocal ischemic insults.

3. Discussion

Varicella Zoster Virus (VZV) is a neurotropic virus which is known to cause a wide spectrum of central nervous system (CNS) complications, including encephalitis, vasculopathy, and myelitis, especially in immunocompromised individuals [8].In this case our patient is an elderly woman with multiple comorbidities, including high-grade B-cell non-Hodgkin lymphoma (NHL) ,autoimmune hemolytic anemia SHTN and T2DM , developed VZV-associated encephalopathy with vasculopathy, ultimately leading to a fatal outcome.

VZV CNS involvement can occur directly through viral invasion as encephalitis, secondary vasculopathy as granulomatous arteritis of large vessels or small-vessel vasculitis, or spinal cord involvement as myelitis [8].Immunosuppression, as seen in patients with hematological malignancies or following chemotherapy can increase susceptibility to VZV reactivation and dissemination [9].In this case, the patient had multiple risk factors, including elderly , underlying NHL, and hypogammaglobulinemia (IgG <360 mg/dL). These conditions have been associated with poor immune response to VZV infection [10]. Notably, she had received immunosuppressive therapy, which may have further predisposed her to CNS complications. The MRI findings shows a diffuse gyral thickening with T2/FLAIR hyperintensities in bilateral parieto-occipital lobes, along with CSF PCR positivity for VZV DNA, confirmed the diagnosis of VZV encephalopathy with vasculopathy .

The radiological manifestations of varicella zoster virus (VZV) vasculopathy present a distinctive spectrum of neuroimaging findings that reflect the virus's predilection for cerebral arteries and its complex pathophysiological mechanisms. Magnetic resonance imaging (MRI) remains the cornerstone diagnostic modality, revealing characteristic patterns that distinguish VZV vasculopathy from other cerebrovascular disorders.

Acute ischemic lesions typically manifest as hyperintense signals on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences, predominantly affecting the territories of medium-sized cerebral arteries. The distribution pattern often demonstrates a predilection for the middle cerebral artery territory, particularly involving the deep white matter and subcortical regions. Notably, the ischemic lesions frequently exhibit a multifocal distribution, reflecting the

segmental nature of VZV-induced arteriopathy, which contrasts sharply with the more uniform patterns observed in typical atherosclerotic stroke.

Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) consistently reveal arterial abnormalities characterized by focal stenoses, irregularities, and beading of affected vessels. These changes predominantly involve the proximal segments of the anterior and middle cerebral arteries, with the characteristic "string of beads" appearance representing alternating areas of constriction and dilatation. Digital subtraction angiography, when performed, demonstrates more subtle changes including vessel wall irregularities and reduced caliber that may not be apparent on non-invasive imaging.

Diffusion-weighted imaging (DWI) provides crucial insights into the acute phase, showing restricted diffusion in areas of cytotoxic edema. The apparent diffusion coefficient (ADC) maps correspondingly demonstrate reduced values, confirming acute ischemia. Importantly, the DWI abnormalities often precede changes visible on conventional T2-weighted imaging, enabling earlier detection and intervention.

Hemorrhagic transformation, while less common, may occur and is best detected using gradient echo sequences or susceptibility-weighted imaging, which demonstrate characteristic blooming artifacts. Additionally, gadolinium-enhanced imaging may reveal blood-brain barrier disruption in affected regions, appearing as areas of enhancement that correlate with inflammatory changes in vessel walls.

The temporal evolution of radiological findings provides valuable prognostic information, with serial imaging demonstrating either resolution of acute changes with appropriate antiviral therapy or progression to chronic ischemic changes in untreated cases, emphasizing the critical importance of early recognition and intervention.

Virological confirmation is necessary for establishment of the diagnosis and it may be done with the help of demonstration of anti-VZV IgG antibody or VZV DNA in the CSF. A positive PCR detection of VZV DNA in cerebrospinal fluid (CSF) supports the diagnosis; however, a negative PCR alone does not rule it out. The diagnosis of VZV vasculopathy can be reliably excluded only when both CSF VZV PCR and CSF anti-VZV IgG antibody tests yield negative results.

VZV vasculopathy is increasingly recognized as a cause of ischemic and hemorrhagic strokes in older adults, with or without skin lesions (zoster sine herpete) [12].Early diagnosis and prompt initiation of intravenous acyclovir are crucial in improving outcomes [8].However, in our patient, despite supportive care, the advanced immunosuppression and severe CNS involvement likely contributed to the poor prognosis. Previous studies have emphasized the poor outcome in patients with VZV CNS vasculopathy when diagnosis and antiviral therapy are delayed [8] .Prolonged Acyclovir prophylaxis for atleast 12 months is recommended in Rituximab-treated patients due to reactivation risk [16].

This case highlights the importance of maintaining a high index of suspicion for VZV CNS involvement in elderly and immunocompromised patients presenting with neurological symptoms and skin manifestations. It also highlights the need for a multidisciplinary approach involving neurology, infectious disease, and hematology teams to optimize management.

Abbreviations

- VZV-Varicella-Zoster virus
- NHL- Non-Hodgkin Lymphoma
- CNS- Central Nervous System
- SHTN- Systemic Hypertension
- T2DM- Type 2 Diabetis Mellitus
- MRI – Magnetic Resonance Imaging
- FLAIR – Fluid-Attenuated Inversion Recovery
- CSF – Cerebrospinal Fluid
- PCR – Polymerase Chain Reaction
- CT – Computed Tomography
- PET-CT – Positron Emission Tomography – Computed Tomography
- CD – Cluster of Differentiation (e.g., CD20)
- BCL2 – B-cell Lymphoma 2
- G-CSF – Granulocyte Colony-Stimulating Factor
- ADA – Adenosine Deaminase

- IVIG – Intravenous Immunoglobulin
- ADC – Apparent Diffusion Coefficient
- DWI/DWMRI – Diffusion-Weighted Imaging / Diffusion-Weighted MRI
- MRA – Magnetic Resonance Angiography
- CTA – Computed Tomography Angiography
- DNA – Deoxyribonucleic Acid
- IgG – Immunoglobulin G
- WHO – World Health Organization
- GCS – Glasgow Coma Scale

4. Conclusion

This case illustrates the devastating impact of Varicella Zoster virus encephalopathy and vasculopathy in a patient with advanced comorbidities , including high grade B-cell NHL and papillary carcinoma of the thyroid . It underscores the need of heightened clinical vigilance for opportunistic infections in immunocompromised individuals and also early diagnostic evaluation and multidisciplinary management to optimize outcomes.

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CONFLICTS OF INTEREST

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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