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Varicella Zoster Infection Complicated by Acute Disseminated Encephalomyelitis and Pneumonitis in an Immunocompetent Patient

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Abstract Primary varicella zoster virus (VZV) infection usually affects children and young adults. Symptoms in immunocompetent patients are generally limited to cutaneous manifestations. Pulmonary and neurological manifestations of primary VZV infection are extremely rare and usually described in immunocompromised patients. Acute Disseminated Encephalomyelitis (ADEM), an immune-mediated inflammatory demyelination event often occurring after a viral infection, has been rarely described as occurring after primary VZV infection. We present a case of a previously healthy adult presenting with primary VZV infection complicated by pneumonitis and neurological involvement. To our knowledge, no similar cases were previously described.

Keywords: *varicella zoster virus, acute disseminated encephalomyelitis, VZV, ADEM, pneumonitis, immunocompetent, chickenpox*

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1. Introduction

Varicella zoster virus (VZV), a DNA virus for whom humans are the only known reservoir, typically manifests as a self-limited cutaneous disease in immunocompetent hosts [1]. It is a member of the Herpesviridae family, and shares structural similarities with other members of this family [2]. Following infection by the respiratory route, viral replication and viremia occur, later manifesting as multiple vesicular skin lesions involving the corneal and dermal skin layers [3]. In the immunocompetent host this vesicular rash ultimately ruptures or is resorbed, and the primary infection is resolved, leaving behind protective antibody titers and cellular immunity [4]. However, the virus remains latent in the spinal dorsal root ganglia and may reactivate in a dermatomal fashion to produce the syndrome of painful rash, the so called "Herpes Zoster" [5]. Rarely, more severe primary infections may occur in adults, associated with significant morbidity [6]. The most frequent sites of non-cutaneous severe involvement are the Central Nervous System (CNS), and neurological abnormalities may include cerebellar ataxia and encephalitis [7,8]. Varicella pneumonitis is another rare, life threatening complication of primary VZV infection. Other complications may include myocarditis, nephritis, bleeding diathesis, and hepatitis [9]. Acute disseminated encephalomyelitis (ADEM) is a multifocal immune-mediated inflammatory disorder of the CNS characterized by widespread demyelination that predominantly involves the subcortical white matter of the brain and spinal cord [10]. Most cases follow viral infection, and rarely vaccination, although a specific pathogen is not usually found. ADEM in immunocompetent adults is extremely rare, and is more common in children and immunosuppressed patients [11].

Here we present a case of a previously healthy 47 year old patient who presented with primary VZV infection and developed two major complications of VZV infection - pneumonitis and ADEM - after completing antiviral treatment for VZV.

2. Case Presentation

A previously healthy, 47 year old patient, married with 4 children and employed as a radiologist was referred to our hospital suffering from severe respiratory distress.

During the month prior to admission three of the patient's children had developed chickenpox infection (i.e., primary VZV infection). All four children were unvaccinated for VZV. The patient was also unvaccinated and has had no history of primary infection. A through history did not reveal any history suggestive of immunocompromise.

4 days prior to admission patient developed a persistent cough and nasal congestion. The following day a vesicular rash appeared on his chest and upper extremities. Two days later, patient started having difficulty breathing, and sought medical attention. Patient initially presented to

the ER of an outside hospital, drowsy and with oxygen saturation levels of 75%. Patient was intubated and rapidly referred to the Medical Intensive Care Unit (MICU) in our hospital.

Patient was admitted while sedated and ventilated. Initial labs showed elevated inflammatory markers, with a leukocytosis of 21.5 $X10^9$/L, with neutrophilia and monocytosis. C-reactive protein (CRP) was 4.3 mg/DL (normal levels - 0 - 0.5mg/DL) and Lactate dehydrogenase (LDH) was 1946 U/L (normal levels 120-246 U/L). Kidney and liver function were normal. Chest X-ray demonstrated a diffuse nodular pattern and CT showed diffuse ground glass opacities and bilateral patchy infiltrates shown in Figure 1. Polymerase chain reaction from patient's serum was positive for VZV.

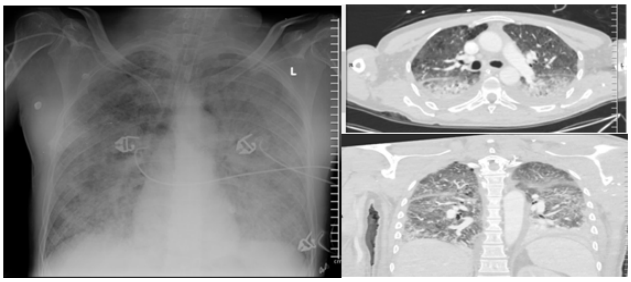

Figure 1. A. anterior posterior chest X-ray demonstrating a diffuse nodular pattern. **B&C**. axial and coronal chest CT demonstrating bilateral patchy infiltrates and diffuse ground glass opacities in both lungs, paracentral emphysema mainly in the upper lobes

A diagnosis of VZV pneumonitis was made and treatment with Acyclovir (10mg/kg/dose q8h) for 14 days was administered. Patient started improving gradually and was ultimately weaned off the ventilator. The patient, who had completed 14 days of Acyclovir treatment, was moved to the internal medical ward for further treatment.

On the ward, the patient was doing well, alert and oriented, communicating and moving all 4 extremities, though suffering from severe myopathy attributed to the protracted ventilation and ICU stay. He still required a small amount of supplemental oxygen. Obscure immunodeficiency was further assessed. Serologies for human immunodeficiency virus were negative and immunoglobulin levels were normal.

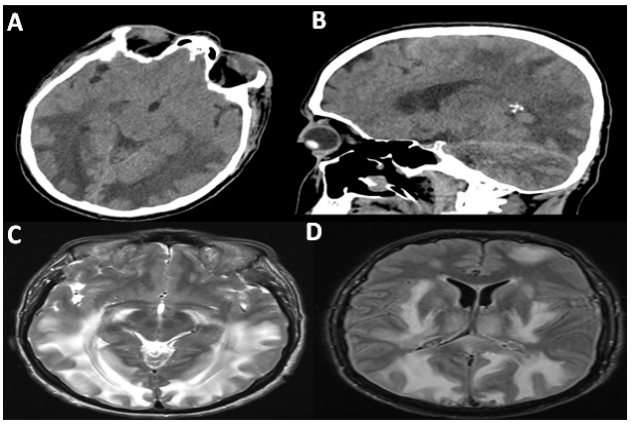

Figure 2. **A, B -** Axial and sagittal view of head computed tomography demonstrating brain edema mainly in the parieto-occipital regions. **C** - Axial T2 weighted MRI and **D** T2 with gadolinium, showing extensive brain edema, of both hemispheres, with a more prominent but not limited to the parieto-occipital region

During one of the evenings, the on-call staff was urgently called to the patient due to decreased consciousness. Patients was found unresponsive, with normal vital signs. Pupils were dilated and non-responsive with a fixed left gaze and repetitive horizontal nystagmus. With a working diagnosis of seizure, patient was given IV diazepam, and when he failed to improve, was administered a loading dose of phenytoin. An urgent computerized tomography (CT) of the head demonstrated severe bilateral brain edema, mostly in the temporo-occipital regions as seen in Figure 2A&B. A brain magnetic resonance imaging (MRI) as shown in Figure 2C&D, revealed diffuse edema of both hemispheres and the cerebellum, with tiny bleeding foci.

The differential diagnosis for these findings consisted of ADEM, varicella zoster encephalitis and posterior reversible encephalopathy syndrome (PRES). While lumbar puncture was not performed due to the prohibitive brain edema, repeat blood PCR for VZV was negative. Patient was thus empirically treated for ADEM with pulse dose corticosteroids a plasmapheresis. A second course of Acyclovir was also started empirically and was stopped after negative blood PCR. Treatment produced a dramatic improvement in his condition and steroids were gradually tapered off.

The patient was later discharged to a rehabilitation facility and has since made a full neurological and respiratory recovery.

3. Discussion

VZV pneumonitis is a life-threatening complication of varicella infection. It is responsible for the majority of morbidity and mortality of patients with varicella [12]. The incidence of VZV pneumonitis in immunocompetent patients is 1:400 cases [13]. In patients requiring mechanical ventilation, mortality rates reach almost 50% despite appropriate aggressive treatment [14].

VZV pneumonitis develops insidiously one to six days after cutaneous lesions appear. Usual symptoms include dry cough and dyspnea, with progressive hypoxemia developing. Chest imaging shows nodular component and diffuse bilateral infiltrates [15]. Treatment includes prompt administration of intravenous acyclovir.

ADEM is an inflammatory process of the central nervous system affecting the brain and spinal cord. Although its pathogenesis is incompletely understood it appears to be an autoimmune disorder, triggered by an environmental stimulus in a genetically susceptible individual [16,17]. Histopathology of ADEM reveals perivascular infiltration of lymphocytes, and perivenous demyelination. The condition typically presents after a preceding viral infection, with herpes viruses being the most common triggers [18].

Diagnosis is based on imaging studies, most commonly an MRI showing multiple bilateral lesions in deep and subcortical white matter, hyperintense in T2, with variable gadolinium enhancement [19]. Cerebrospinal findings may include lymphocytic pleocytosis with elevated or normal CSF protein [20]. The diagnosis should be considered in patients with a multifocal neurological presentation following a viral infection.

Treatment is based on immunosuppression, most commonly high dose glucocorticoids, intravenous immunoglobulin treatment, or plasma exchange [21]. Most adults with ADEM will improve with the treatment, with complete recovery in up to 40% of patients [22].

This case describes a patient who developed severe neurological symptoms after primary VZV infection. While definitive diagnosis is impossible, mainly due to the fact that a lumbar puncture was deemed prohibitively risky in this instance, the clinical course, MRI findings and dramatic reaction to treatment all support the probable diagnosis of ADEM.

To our knowledge, no previous cases have described both extra-cutaneous complications of primary VZV infection and a para-infectious neurological sequela seen in our case. The rarity of these conditions is underlined by the immunocompetent status of our patient, who has not had any suggestive events before, or - to the best of our knowledge - since.

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