Case Report

# Thrombotic Thrombocytopenic Purpura due to Varicella-Zoster Virus Meningoencephalitis in an Immunocompetent Patient

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## Abstract

Varicella-zoster virus (VZV) can cause variable disease states in individuals with intact and compromised immune systems. Both meningoencephalitis and thrombotic thrombocytopenic purpura (TTP) are uncommon, life-threatening entities associated with VZV. There are few reported cases of TTP due to VZV and this may be the first case of TTP due to VZV meningoencephalitis confirmed through lumbar puncture. The literature tends to emphasize that this pathology mostly occurs in immunocompromised hosts. Here, we present a unique case of TTP due to VZV meningoencephalitis in a patient that was immunocompetent.

**Keywords:** Meningoencephalitis, thrombotic thrombocytopenic purpura, varicella zoster virus

## Introduction

Varicella-zoster virus (VZV) causes a spectrum of illness in humans. Primary infection through invasion of the dorsal root ganglion produces a vesicular rash. Reactivation of latent VZV is termed "herpes zoster" which results in a painful, dermatomal rash.[1] VZV is also known to cause meningoencephalitis or inflammation of the brain parenchyma and the meninges; this entity is thought to be more common in immunocompromised individuals.[2] Fever, headache, confusion, and seizure are the common manifestations of VZV meningoencephalitis; of note, a rash is not always present.[3]

Thrombotic thrombocytopenic purpura (TTP) is a medical emergency characterized by fever, microangiopathic hemolytic anemia, thrombocytopenia, and renal and neurologic dysfunction. This syndrome is triggered by a congenital or acquired decrease in a disintegrin and metalloprotease with thrombospondin type-1 motif member-13 (ADAMTS13), a metalloproteinase that cleaves von Willebrand factor (VWF). The diminished activity of ADAMTS13 causes the accumulation of large platelet-VWF multimers and the formation of platelet-rich microthrombi that creates end-organ damage and the classical pentad.[4] There are only two other reported cases in the literature of VZV causing TTP.[5,6]

## Case Report

A 44-year-old female was brought to the emergency department for 3 days of fatigue, vomiting, weakness, and altered mental status. The patient visited a walk-in clinic 1 week prior for "body pains" and was prescribed acetaminophen, oseltamivir, and meclizine. She denied fever, chest pain, shortness of breath, cough, abdominal pain, dysuria, recent travel, sick contacts, or rashes. The past medical history included hypertension and diabetes mellitus type 2 (hemoglobin A1c 7.3%). She did not take any medications, was of Haitian origin, and had no toxic habits.

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Initial vital signs were within normal limits. The physical examination was notable for mucosal pallor and petechiae on the chest. Cardiopulmonary, neurologic, and digital rectal exams were all unremarkable.

Initial laboratory findings were significant for white blood cell (WBC) count 10,450 cells, hemoglobin 7.8 g/dL, platelet count 10,000 cells, creatinine 0.99 mg/dL, lactate 1.7 mmol/L, lactate dehydrogenase 1379 U/L, haptoglobin < 10 mg/dL, and fibrinogen 470 mg/dL. Peripheral blood smear showed 10–15 schistocytes per high-powered field, many microspherocytes, and rare platelets without clumping. Urinalysis showed gross blood and few bacteria. Urine toxicology screen, severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (PCR), Influenza A and B PCR, and human immunodeficiency virus 1 and 2 antigen/antibody were all negative. Electrocardiogram showed sinus tachycardia. Initial computed tomography (CT) of the head showed no acute intracranial pathology. Chest X-ray showed no acute pulmonary process.

The patient had a convulsive seizure in the emergency department; she was given lorazepam and midazolam and was intubated for airway protection. The repeat temperature was 103F and new blood work was notable for a WBC count 19,500 cells, hemoglobin 5.8 g/dL, creatinine 1.6 mg/dL, and lactate 7.5 mmol/L. The patient was given one unit of packed red blood cells, two units of platelets, four units of fresh frozen plasma (FFP), 3 L of lactated ringers solution, vancomycin, piperacillin-tazobactam, acyclovir, and levetiracetam. The calculated PLASMIC score was seven (72% risk for ADAMTS13 deficiency) and plasma exchange was initiated with 11 units of FFP. ADAMTS13 activity was found to be <2% and shigella toxin was negative. The patient was admitted to the intensive care unit for TTP.

Plasma exchange, levetiracetam, vancomycin, and acyclovir were continued, and cefepime and intravenous methylprednisolone were started. Electroencephalogram did not reveal seizure-like activity. Repeat CT head showed nonspecific, mild sulcal effacement in the bilateral high frontal lobes, which can be seen in meningitis [Figure 1]. Lumbar puncture was performed, and cerebrospinal fluid (CSF) showed glucose 106 mg/dL, protein 73 mg/dL, and 10 WBC (9 neutrophils and 1 lymphocyte). BioFire® FilmArray® meningitis-encephalitis (ME) panel was positive for VZV. CSF culture, cryptococcal antigen, *mycobacterium tuberculosis* PCR, and stain for acid-fast bacilli were all negative. Acyclovir was continued for 14 days, and plasma exchange was continued for 8 days.

The patient was extubated on hospital day 4 and her mental status gradually improved. Methylprednisolone was switched to prednisone with a planned outpatient taper. Trimethoprim-sulfamethoxazole and fluconazole were started as prophylaxis for invasive fungal infections. Rituximab was deferred until after the completion of steroid therapy to minimize immunosuppression. The patient's platelet count recovered, and she was discharged with outpatient appointments for hematology and neurology.

## Discussion

There are two other case reports of TTP due to VZV. In the first case by Satoh *et al*., a 19-year-old female presented with a painful, bleeding vesicular rash followed by nausea, fatigue, and headache.[5] Labs showed hemoglobin 5.5 g/dL, platelet count 10,000 cells, negative anti-VZV immunoglobulin M (IgM) titer, and positive IgG titer 1:640. The patient was given acyclovir, heparin, and plasma infusion and her symptoms resolved; however, the platelet count only normalized after the introduction of prednisolone and plasma exchange. She survived without relapse.

In the second case by Xu and Ritchie, a 68-year-old female with multiple myeloma presented with fever, delirium, and epigastric pain.[6] She was found to have thrombocytopenia, acute renal failure, and hemolysis with schistocytes on a peripheral smear. ADAMTS13 level was 70% (normal). Plasmapheresis was administered for 11 days. Serum VZV PCR was persistently positive, and acyclovir was started on hospital day 11. No lumbar puncture was performed given severe thrombocytopenia. The patient died on hospital day 25.

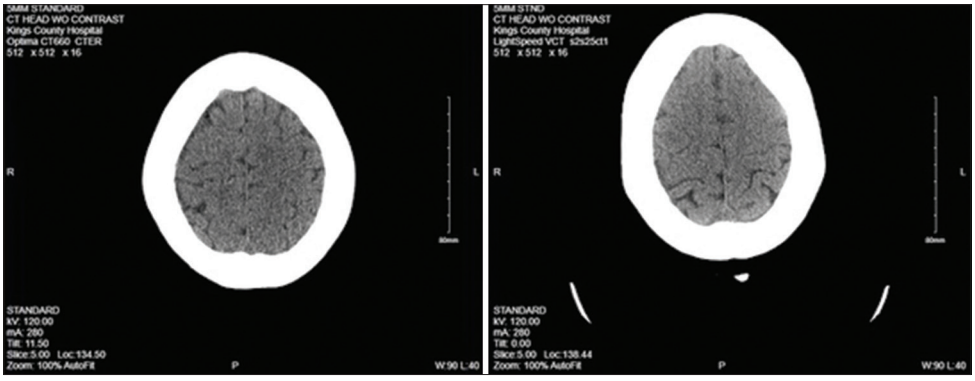


**Figure 1:** Initial CT head showed no acute intracranial pathology (left). Repeat CT head showed nonspecific, mild sulcal effacement in the bilateral high frontal lobes, which can be seen in meningitis (right). CT: Computed tomography. Source: Zachary Mostel, MD, Department of Medicine, NYC Health and Hospitals/Kings County Hospital Center, Brooklyn, NY, USA

Immune status may be a critical factor in determining the outcome. The immunocompromised patient succumbed to her illness while the immunocompetent patients both responded favorably to treatment. Only one of these three cases presented with classic zoster lesions; VZV infections of the central nervous system are without skin lesions in 44%–68% of cases.[7,8]

The interpretation of the CSF findings from this case has several limitations. First, the authors believe the BioFire® ME panel result to be a true positive for VZV. A meta-analysis evaluating the validity of the BioFire® ME panel found one false positive and one false negative out of 78 cases of VZV ME (98.7% sensitivity and specificity).[9] It remains unclear whether the VZV in the CSF was driving the TTP, a complication of immunosuppressive therapy, or reactivation of latent virus without pathogenicity. Positive results for human herpesviruses may be due to the detection of latent virus in lymphocytes in the CSF due to critical illness or immunocompromise.[10] It ultimately remains unclear if the VZV in the CSF was pathogenic, as the patient was immediately started on both acyclovir and plasma exchange with the resolution of her illness.

## Conclusion

TTP secondary to VZV is an uncommon pathology. This may be the first case of TTP due to VZV meningoencephalitis confirmed through lumbar puncture. Our case serves as an invaluable example of this entity occurring in an immunocompetent host. It can be difficult to determine whether VZV and other herpesviruses detected in the CSF are actively pathogenic or latent.

### Research quality and ethics statement

The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that their name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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