Thrombotic Microangiopathy Secondary to Disseminated Varicella Zoster Virus Infection in an Adult Patient

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Patient: Male, 43-year-old
Final Diagnosis: Atypical hemolytic uremic syndrome • thrombotic microangiopathy • thrombotic thrombocytopenic purpura
Symptoms: Fever • purpuric skin lesions • rash • seizure
Medication: —
Clinical Procedure: Blood transfusion • immunoglobulin therapy • plasma exchange
Specialty: Hematology • Infectious Diseases • General and Internal Medicine

Objective: Unusual clinical course
Background: Thrombotic microangiopathy (TMA) is a life-threatening condition caused by small-vessel platelet microthrombi. While various disease triggering factors, including infections, have been well described, there have been few reports of an association between TMA and varicella zoster virus (VZV) infection. VZV infection is rare among people age 20 and older, and infection-induced TMA is mostly reported in the pediatric age group. We report a case of TMA induced by a disseminated VZV infection in an adult.

Case Report: A 43-year-old man presented with a 3-day duration of fever, headache, vomiting, and bloody diarrhea. He also reported body rash after a recent contact with a few roommates with chickenpox. On presentation, the patient developed convulsive seizures. His laboratory test results were significant for acute kidney injury (AKI) and thrombocytopenia. Atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) were suspected but further diagnostic testing was negative. The treatment plan included acyclovir, therapeutic plasma exchange, and high-dose oral prednisolone (1.5 mg/kg). The clinical and biochemical profile significantly improved, and the patient was discharged home.

Conclusions: TMA is a life-threatening hematological emergency with a high mortality rate. Compared to the pediatric population, VZV infection tends to be more severe in the adult age group. This case demonstrates that a high index of suspicion for TMA in adult patients with VZV who present with thrombocytopenia, even when there is no definitive diagnosis, can result in early management with favorable outcome.

Keywords: Atypical Hemolytic Uremic Syndrome • Hemolytic-Uremic Syndrome • Purpura, Thrombotic Thrombocytopenic • Thrombotic Thrombocytopenic Purpura, Acquired • Varicella Zoster Virus Infection • Thrombotic Microangiopathies

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Deep tendon reflexes were normal. Motor examination and He was alert and oriented with no focal neurologic deficits. Bilateral coarse crepitations were noted on chest auscultation. cal ulcers, and ecchymosis over the right arm and abdomen. lopapular rash involving the palms and soles (jaundiced, with a generalized, purpuric, non-blanching rash (90/60-120/80 mmHg), SpO2 92% (95-99%) on 2 L/min ox ygen via nasal cannula. On examination, he appeared ill and ry rate 17/min (12-18/min), blood pressure 138/81 mmHg (36.6-38.1°C), heart rate 101/min (60-100/min), respirato on presentation, the patient’s temperature was 36.7°C (36.6-38.1°C), heart rate 101/min (60-100/min), respirator On examination, he developed convulsive seizures. His past med ical history consisted of well-controlled hypertension, type 2 diabetes mellitus, and psoriasis, on oral steroids. His medica Cough, headache, vomiting, and bloody diarrhea. He also reported body rash after recent contact with a few roommates with chickenpox 15 days before his illness started. On presentation, the patient developed convulsive seizures. His past med ongulation. A few reports, such as Basnayake (2020) [6], showed an association between TMA and VZV in fe cination, and the majority were in the pediatric age group. In the present report, we discuss a case of TMA induced by a dis seminated VZV infection in an adult with a diagnostic chal lenge but a successful outcome. Laboratory results are presented in Table 1. Blood and stool cultures were negative. In addition, serology for human immunodeficiency virus (HIV) was negative. Further testing for complements and ADAMTS13 enzyme deficiencies were negative. ADAMTS13 activity assay was nor mal. The shiga-like toxin assay was negative. IgM and IgG immunoglobulins were identified on varicella zoster virus se rolgy assays. Computed tomography of the head was normal. Chest radiograph demonstrated prominent bilateral interstitial lung markings and central vessels, suggesting mild congestive changes. The renal ultrasound was normal. Atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) were suspected, but further di agnostic testing was negative. After Hematology and Nephrology consultation, 2 units of packed red blood cells and 4 units of fresh frozen plasma were administered in preparation for thera HUS described 3 decades later by Gasser et al [2]. TMA has been associated with various triggering factors, including inf ections, illicit drug use, neoplasms, connective tissue disor ders, and pregnancy [3-5]. Direct endothelial injury is the pro posed pathogenesis mechanism for the development of TMA. It is characterized by thickening of the arterioles, endotheli al swelling, intraluminal platelet thrombi, and fragmentation of red blood cells (RBC) as blood flows across the partially oc included microcirculation. 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The patient had a total of 9 plasma exchange sessions, and his clinical and biochemical profiles significantly improved by day 5 of treatment, almost normalizing upon completion of plasma exchange therapy. His oxygen therapy was discontinued. His volume status and renal function improved, and he regained baseline status and was discharged home. Eculizumab was considered; however, it was not started as the patient showed an excellent response to treatment.

**Outcome and Follow-Up**

Upon discharge, the patient had improved, and his renal functions, platelet count, and LDH levels had normalized (Figure 2). After a 21-day stay in the hospital, the patient was released on a tapering dose of steroids with a follow-up arranged in 2 weeks. Unfortunately, the patient traveled to his home country and was lost further follow-up.

**Discussion**

Viruses are important in the development of TMA; many are only linked to HUS or aHUS, but some can cause TTP. The pathophysiology of TMA induced by viruses is unknown. On the other hand, direct endothelial cell damage appears to be an important pathology trigger [7-9]. Furthermore, host genetic or environmental susceptibility factors may provide a favorable environment for viruses to initiate the chain of events that result in TMA’s clinical manifestations. Although certain reports of viral-related TMA are based on anecdotal evidence, such correlations cannot be ruled out [7-10].

Varicella is predominantly a childhood disease characterized by vesicular exanthema frequently accompanied by fever and malaise. Human VZV disseminates to the viscera during viremia and multiplies in reticuloendothelial tissues. Varicella usually manifests as mild to moderate illness, but serious complications (eg, meningoencephalitis, meningitis, vasculitis affecting small or large vessels, pneumonia, and hemorrhages) can arise. There is only 1 previous report of this type of HUS following varicella infection [11].

Primary VZV infection in adults has a more severe presentation, including interstitial pneumonia, in comparison to younger age groups. In addition, the infection produces severe, disseminated diseases in immunocompromised individuals. More
than 90% of people are infected before adolescence, with 13-16 cases per 1000 people per year. In tropical climates, however, VZV infection occurs later in life. Varicella has a peak incidence in the late winter and spring, and epidemics tend to occur every 2-5 years [12,13].

Fever and a self-limiting rash on the skin, and occasionally the mucosa, are symptoms of varicella. Headaches, malaise, and a loss of appetite are also common. Macules are the first signs of the rash and rapidly progress to papules, followed by a vesicular stage and crusting of lesions. VZV is highly infectious, and transmission occurs by direct contact with skin lesions or respiratory aerosols from infected individuals. Central nervous system complications include self-limiting cerebellar ataxia in 1 in 4000 cases, meningitis, meningoencephalitis, and vasculopathy. Stroke may occur months after varicella, secondary to VZV vasculopathy, and are not always easy to diagnose [12,13].

Our patient presented with a varicella infection associated with macular rash and fever followed by renal failure and seizure. He was investigated for TTP, but ADAMTS13 testing was reported to be normal. Given the presence of MAHA, thrombocytopenia, and renal failure, we believe that this was a case of TMA, with a high probability of an atypical form of HUS. The patient showed improvement after receiving multiple sessions of plasma exchange and steroids.

New algorithms for managing MAHA, thrombocytopenia, and renal failure have developed because the frequency of different kinds of HUS varies by age [12,13]. In our case, the negative E. coli 0157: H7 shiga-like exotoxin and the shiga toxin assays excluded atypical HUS, and TTP was excluded by the lack of severe ADAMTS13 deficiency, resulting in lack of a definitive diagnosis. The present consensus is that plasma exchange for 5 days should be used as a first-line treatment [12]. If an inadequate response to medication fails to normalize LDH, platelet count, or lower creatinine level by more than 25%, eculizumab therapy should be started, but our patient’s LDH and creatinine levels improved despite the lag in platelet count improvement.

Figure 2. Daily biochemical markers trend with each day of therapeutic plasma exchange (TPE) and steroids. X-Axis: days of therapy from admission to discharge. (A) Y-Axis: True lab values of lactate dehydrogenase (LDH) and platelets. (B) Y-Axis: true lab values of serum creatinine.

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Conclusions

TMA is a life-threatening hematological emergency with a high mortality rate if not identified and treated early. Identifying the etiology may help guide the management.

VZV infection tends to be more severe in the adult age group compared to the pediatric population. Many viral infections are known to be associated with TMA [4,7].

To the best of our knowledge, this is the first reported case of TMA as a complication of VZV infection in an adult. A high index of suspicion for TMA in adult patients with VZV who present with thrombocytopenia, even when there is no definitive diagnosis, can result in early management with favorable outcome.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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