Clinical Case Report

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Thrombotic thrombocytopenic purpura and hemophagocytic lymphohistiocytosis in an elderly man

A case report

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Abstract

Rationale: Thrombotic thrombocytopenic purpura (TTP) and hemophagocytic lymphohistiocytosis (HLH) are rare hematologic conditions and have high mortality. Both TTP and HLH result from deregulation of the immune system. There are no published reports of coexisting TTP and HLH in elderly patients.

Patient concerns: A 67-year-old Asian male presented with altered consciousness and fever for 2 days. Physical examination revealed markedly pale, mild icterus with petechiae and purpura. Initially, TTP was recognized in this patient. Bone marrow studies are suggested for evaluating elderly patients to assess specific causes, especially infection and neoplasm.

Diagnoses: The TTP was diagnosed based on typical history-related symptoms and a specific laboratory result of very low ADAMTS13 level. The diagnosis of HLH was determined after detection of high levels of ferritin and lactase dehydrogenase, which were confirmed by the presence of hemophagocytosis in the bone marrow.

Interventions: Systemic corticosteroids and plasma exchange were initiated as specific treatment of the patient.

Outcomes: The patient died in 3 weeks from ventilator-associated pneumonia.

Lessons: The HLH should be tested using bone marrow studies and specific laboratory tests in patients with TTP.

Abbreviations: ADAMTS13 = a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, member 13, CMV = cytomegalovirus, CT = computed tomography, EBV = Epstein-Barr virus, HLH = hemophagocytic lymphohistiocytosis, IL = interleukin, LDH = lactate dehydrogenase, PEX = plasma exchange, TTP = thrombotic thrombocytopenic purpura, VAP = ventilator-associated pneumonia.

Keywords: bone marrow, elderly patients, hemophagocytic lymphohistiocytosis, plasma exchange, thrombotic thrombocytopenic purpura

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening hematologic condition. The annual incidence is 1 new case per million people, and the mortality rate exceeds 90% in the absence of rapid, appropriate management.[1,2] The onset of TTP almost always occurs in adults aged between 30 and 40 years, and the sex ratio is 1:3.[2] TTP is characterized by a history of multiorgan ischemic symptoms mainly targeting the brain and kidneys and caused by disseminated microvascular platelet-rich thrombi aggregated in small arterioles and typical biologic abnormalities of severe thrombocytopenia ($<30 \times 10^9$/L), and microangiopathic hemolytic anemia.[1] The current definition is completed by the presence of a deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), a biologic marker specific for TTP.[3,4] There are 2 clinical forms of TTP, congenital, and acquired. Acquired TTP is commonly caused by inhibitory autoantibodies directed against ADAMTS13. However, there are a wide variety of predisposing factors associated with an increased risk of TTP, including female sex, black race, obesity, and *HLA-DRB1*11*.[5] The pathophysiology of TTP comprises the relationships among immune processes, particularly autoimmunity, which is widely recognized as the primary pathophysiologic mechanism, together with cytokine and complement dysregulation. In addition, a recent review identified the role played by activated ADAMTS13-specific self-reactive $CD4^+$ T cells, which enhance the production of autoantibodies to ADAMTS13-specific B cells. ADAMTS13 activity affects disease severity and relapse as well as treatment intolerance.[3]

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon syndrome, and a potentially fatal extreme inflammatory condition caused by excessive immune activation and severe

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hypercytokinemia, leading to an increase in macrophage activity and cytokine release, resulting in tissue damage and multiple organ failure. HLH can be subcategorized into primary and acquired disorders, triggered by various events that disrupt immune homeostasis, for example, infection, mostly viral, or other immunologically activating events, illness, autoimmune disease, and lymphoma.[6,7] The incidence is approximately 1.2 cases per million people per years. Secondary HLH is more common in adults than in children or elderly people.[8,9] The diagnosis of HLH is based on clinical features, lab results, and the presence of hemophagocytosis. The clinical manifestations include fever, hepatosplenomegaly, and weight loss. Laboratory tests show bicytopenia or pancytopenia, hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, high-soluble interleukin (IL)-2-receptor levels, and low or absent natural killer cell activity. The standard for diagnosis remains the presence of hemophagocytic macrophages in histologic specimens, such as bone marrow, liver, spleen, and lymph nodes.[6]

The TTP and HLH are likely underrecognized and have similarly high rates of morbidity and mortality. Early recognition is important for the best treatment. Herein, the authors report the rare occurrence of HLH associated with TTP in an elderly man.

2. Case report

A 67-year-old Asian male, with a medical history of well-controlled diabetes mellitus and hypertension, presented with alteration of consciousness for 2 days. He also reported fatigue, loss of appetite, nausea, weight loss of about 5 kg, low-grade fever, and dark urine over a 2-week period previously. The patient did not use herbal or alternative medicine. He was admitted to Bangkok Hospital Hat Yai.

On the day of admission, the patient was lethargic with a temperature of 38.5°C, blood pressure of 140/90 mm Hg, pulse rate of 110 beats/min, and respiratory rate of 24 breaths/min. Physical examination revealed markedly pale, mild icterus with petechiae, and purpura at the peripheries. Neurologic examination revealed drowsiness without neurologic deficit.

Initial laboratory studies showed severe anemia with hemoglobin 7.5 (13.0–18.0) g/dL, white cell count 8.4 (4.5–10.0) $\times 10^9$/L (neutrophils 72.5%, lymphocytes 18.5%, monocytes 7.1%, eosinophils 1.6%, basophils 0.3%), and platelet count 7 (150–450) $\times 10^9$/L. A blood smear showed schistocytes with a variety of shapes, small triangular red cell fragments (triangulocytes), and larger, crescent-shaped red cell fragments (helmet cells) (Fig. 1A, B). The results of a coagulogram included prothrombin time 12.5 (10–14) seconds, activated partial thromboplastin time 23.7 (22–32) seconds, and fibrinogen levels 342.8 (200–400) mg/dL. Direct Coomb test was negative. Complete metabolic panels showed serum creatinine 2.15 (0.67–1.17) mg/dL, total bilirubin 14.6 (0–1.2) mg/dL, direct bilirubin 2.45 (<0.3) mg/dL, aspartate transaminase 11,742 (0–40) U/L, alanine transaminase 4084 (0–41) U/L, alkaline phosphatase 124 (40–130) U/L, and lactate dehydrogenase (LDH) 2046 (135–225) U/L. Serologic tests for hepatitis B surface antigen, anti-hepatitis C virus, anti-human immunodeficiency virus, anti-cytomegalovirus (CMV), and anti-Epstein-Barr virus (EBV) antibodies were negative. Blood cultures showed no growth. Serum ADAMTS13 was 9%. A chest radiograph and computed tomography (CT) scan of the brain were normal.

The initial diagnosis was TTP. Systemic corticosteroid and plasma exchange (PEX) with 1.5 plasma volumes of fresh frozen plasma per day were initiated as specific treatment. He was also started on empiric broad-spectrum antibiotics. The patient responded to therapy, with neurologic improvement and platelet count increased to 54×10^9/L.

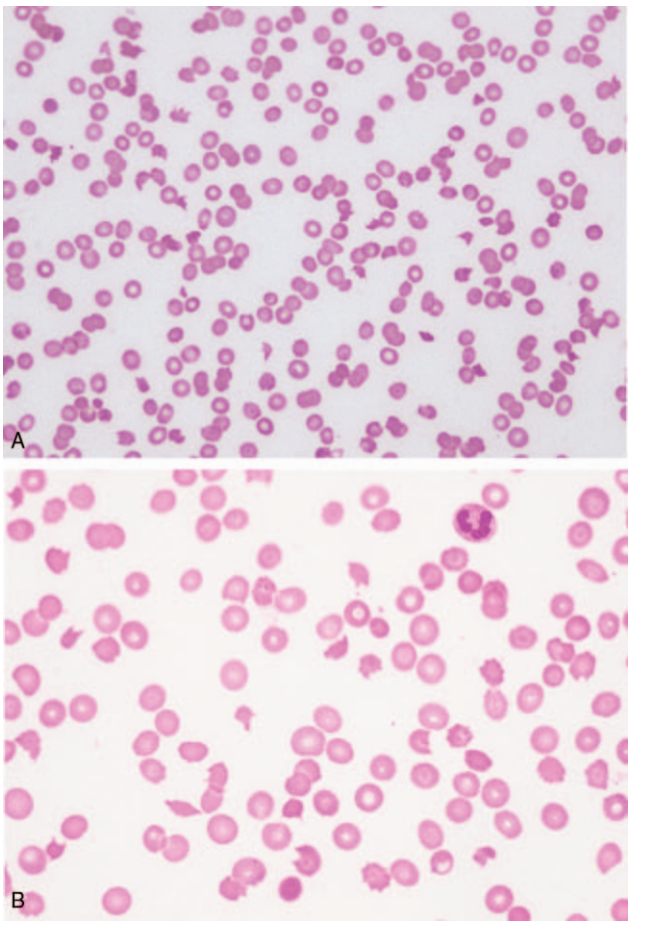

Figure 1. Peripheral blood smear. (A) Varying shapes of schistocytes with thrombocytopenia (×10 magnification). (B) Crescent-shaped helmet cells and small triangulocytes (×40 magnification).

Bone marrow studies were conducted to determine the cause of TTP in this elderly patient. Bone marrow aspiration showed prominent hemophagocytosis, characterized by numerous bland-appearing histiocytes containing phagocytosed erythrocytes within the cytoplasm, and some hematopoietic cells engulfed by macrophages (Fig. 2A, B). Additional laboratory data revealed ferritin level 84,455 (30–400) mg/dL and LDH 10,895 U/L. Provisionally, further diagnosis of HLH was made. Of note, tumor screenings were negative in CT scans of the neck, chest, and whole abdomen. Other tests, bone marrow culture, and blood tests for connective tissue disease, were all negative.

On day 4 of hospitalization, the patient developed generalized tonic-clonic seizure. CT scan of the brain was repeated, with unremarkable findings. He developed worsening respiratory failure necessitating endotracheal intubation and mechanical ventilation. He had a high-grade fever and increased sputum production; ventilator-associated pneumonia (VAP) then became a concern. The patient had received a combination of antibiotics (meropenem, colistin, and ampicillin-sulbactam) for the infection. Sputum cultures were positive for *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. The patient remained clinically stable with daily PEX. On day 17 of hospitalization, he went into septic shock owing to VAP and

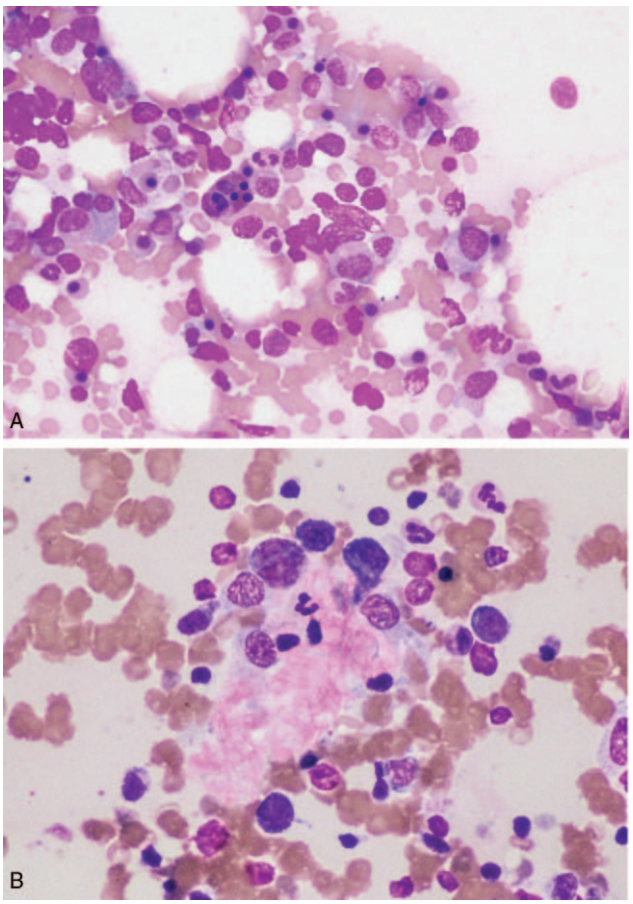

Figure 2. Bone marrow aspiration. (A) Prominent hemophagocytosis, characterized by bland-appearing histiocytes containing phagocytosed erythrocytes and some hematopoietic cells engulfed by macrophages (×40 magnification). (B) Reticular cells with ingestion of white blood cell and lymphocytes (×60 magnification).

multiple vasopressors were initiated. His platelet count dropped to 8×10^9/L despite continued PEX. The patient died after experiencing sudden cardiac arrest 3 weeks after the diagnosis of TTP and HLH.

3. Discussion

We report the case of an elderly patient diagnosed with TTP, based on standard clinical pentad criteria and confirmed using assays of ADAMTS13 activity,[2,3] associated with secondary HLH. It has been long known that acquired TTP is typically found in relatively young female adults (30–40 years of age), in contrast to our case in an elderly male.[2] In addition, secondary elderly onset HLH is quite rare.[9]

The TTP and HLH often occur as a result of pathologic immune activation in response to several triggers. The most frequently noted overlapping triggers include neoplasm (especially hematologic malignancy), infection (particularly viruses such as EBV and CMV), and autoimmune disorders.[3,6,10] Hence, these features should always trigger a clinician's suspicion of secondary causes in both of these rare conditions. However, there were no specific causes in this case, despite extensive investigation. Little is known regarding whether the exact association between TTP and HLH is causative or merely coincidental.

There have been reports of coexisting TTP and HLH triggered by infection, an autoimmune disorder, and therapy.[11–14] The authors hypothesize that the basis for the strong relationship between TTP and HLH is immune dysregulation. Innate and adaptive immunities have roles in both TTP and HLH. ADAMTS13 is a critical component in the pathophysiology of TTP.[3,4] ADAMTS13 can stimulate complement pathways and inflammatory cytokines, mainly IL-6 and IL-10, and autoreactive B and T cells.[4,15] HLH causes hyperactivity due to monocytes and macrophages, which can initiate the activation of a cytokine storm. The most common cytokines are IL-6, IL-10, IL-18, tumor necrosis factor α, and interferon γ.[7] Regarding the immune abnormalities in TTP and HLH, there is some overlapping immune dysregulation, which probably constitutes the main component of the association between these 2 diseases.

The standard treatment of TTP is PEX, which removes anti-ADAMTS13 neutralizing autoantibodies and harmful cytokines from the circulation and replenishes ADAMTS13.[1] An additional adjunctive therapy is glucocorticoids, which reduces production of ADAMTS13 autoantibodies and promotes a reduction in the frequency of PEX.[1,16] In addition, recent studies have shown the benefits of rituximab, a chimeric monoclonal antibody directed against CD20 located on the cell surface of mature B cells. The effect of rituximab is to reduce the risks of exacerbation and relapse, and it may speed up the response to therapy.[1,4,16]

Our patient was initially treated with PEX and a high dose of corticosteroids, and he responded well in the short term. There were several possible factors affecting treatment. First, the patient had a co-existing life-threatening disorder, HLH, which stimulates persistence of immune hyperactivity, particularly hypercytokinemia and monocyte hyperactivity, resulting in the development of thrombotic microangiopathy.[10] Furthermore, the patient had complications of TTP itself, including multiple organ dysfunction syndromes and disseminated intravascular coagulation that can trigger reactive HLH.[13,14] Second, PEX can stimulate the release of cytokines from neutrophils during their passage through materials, which can initiate reactive HLH, which was reported after 2 weeks of treatment.[14] In addition, elderly patients, as in this case, can develop PEX-related complications, including bleeding, infection, and hypotension; these factors can affect treatment outcomes.

4. Conclusion

The diagnosis of TTP is challenging owing to the rarity of this disease, which can cause delayed management, thus affecting prognosis. Co-incidence of TTP with reactive HLH is a sporadic condition that makes for worse disease outcomes and increased morbidity and mortality; furthermore, it is refractory to treatment. However, early and extensive investigation in the diagnosis of HLH, along with further insight into the pathophysiology of these disease entities, will decrease complications and improve the survival and quality of life for patients in remission from TTP.

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