

# Fatal Thrombotic Thrombocytopenic Purpura Coexisting with Bacterial Infection: A Case Report

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**Abstract-** Thrombotic thrombocytopenic purpura (TTP) has a varied clinical presentation with possibly rapid deterioration. Neurological involvement in TTP is common. A 75-year-old woman with TTP presented with diffuse ischemic stroke and fatal multi-organ damage following bacterial infections. Coexisting bacterial infection, cardiac dysfunction and diffuse cerebral infarction may be poor prognostic factors for TTP patients.

**Key Words:** Thrombotic thrombocytopenic purpura, Infection, Stroke

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## INTRODUCTION

The classic description of thrombotic thrombocytopenic purpura (TTP) includes a pentad of thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, neurological abnormalities and fever. It is often described as protean and fleeting neurological symptomatology with an acute but fluctuating clinical course<sup>(1)</sup>. There is high shear stress in the arterioles and capillaries and this enhances the cleavage of von Willebrand Factor (vWF) by the protease ADAMTS13 (a disintegrin and metalloprotease with thrombospondin domains)<sup>(2)</sup>. If there is genetic mutation or immune-mediation of ADAMTS13 deficiency, ultra-large von Willebrand multimers will interact with activated platelets in these areas. Failure to cleave the vWF-platelets strings is thought to cause widespread platelet

microthrombosis<sup>(3)</sup>. Microthrombosis of the brain occurs in 50%-80% of TTP patients and accounts for the frequent presenting neurological symptoms, such as alerted mental status, headache, focal neurological abnormalities or seizure<sup>(4)</sup>. Though the use of plasma exchange has significantly reduced the morbidity and mortality of TTP, sudden death remains a medical challenge in managing these patients. Ischemic injury to the heart and conduction system is the most likely mechanism of sudden death<sup>(5)</sup>. Fatal TTP has been associated with sudden cardiac arrhythmia<sup>(6,7)</sup>, autoimmune disease<sup>(8)</sup>, caesarean section<sup>(9)</sup>, HIV infection<sup>(10)</sup>, ciprofloxacin use<sup>(11)</sup>, and methamphetamine<sup>(12)</sup> or cocaine abuse. Although it is well established that TTP may arise in association with infection<sup>(13,14)</sup>, there are few published studies that discuss the association of fatal TTP with infection. Herein, we report a patient with multiple cerebral infarctions

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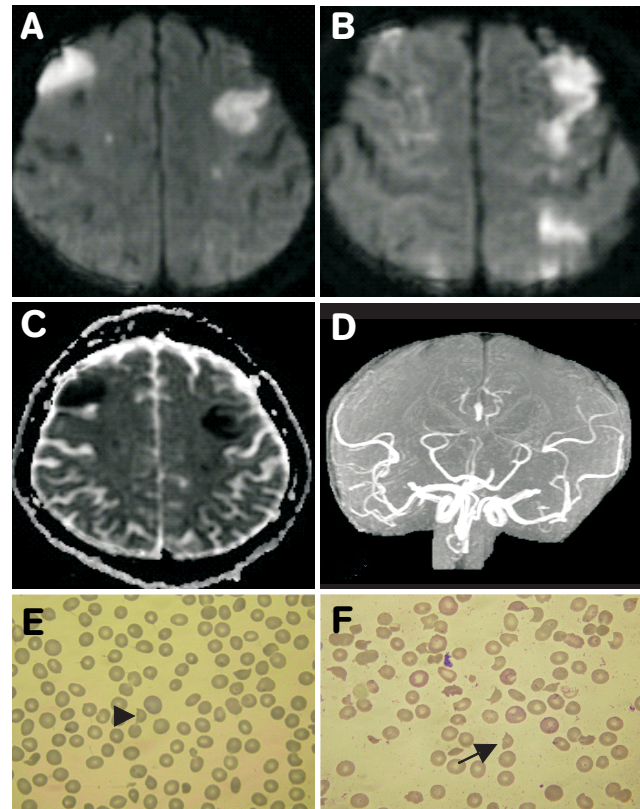
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and fatal TTP that coexisted with bacterial infection.

### CASE REPORT

A 75-year-old Taiwanese woman with regular anti-hypertensive treatment and occasional analgesics for intermittent headaches for years, presented with progressive headache, general malaise and alerted mental status over a period of three days. There was no other major medical or surgical history.

On examination, her blood pressure was 142/101 mmHg, pulse rate 120 beats/min, body temperature 37.4°C, and respiration rate 22 breaths/min. Mildly icteric scleras and tenderness without rebound over the right upper abdomen were noted. The Glasgow coma scale was E3V2M6. There were equal and minimally reactive pupils, conjugated eye deviation to the left side, and right hemiplegia. The chest X-ray showed bronchiectasis, cardiomegaly, and a widening mediastinum. The electrocardiogram (ECG) was unremarkable. Abnormal hemograms included mild leukocytosis with left shift, normocytic anemia and severe thrombocytopenia (Table). Abnormal blood chemistries comprised aspartate aminotransferase 92 U/L (normal, 10-32), urea nitrogen 50 mg/dL (normal, 6-20), creatinine 1.8 mg/dl (normal, 0.5-0.9), total bilirubin 2.5 mg/dl (normal, 0.1-1.0), direct bilirubin 0.4 mg/dl (normal, 0.0-0.3), and erythrocyte sedimentation rate 39 mm/h (normal, 0-20). The urinalysis showed white blood cells 10-13 in high power field but no bacteria were found. On diffusion weighted (Figs. A and B) and apparent diffu-



**Figure.** Multiple hyperintense lesions on diffusion weighted imaging (A, B) and hypointense lesions on apparent diffusion coefficient imaging (C) over bilateral cerebral hemispheres suggested diffusely acute cerebral infarctions. Magnetic resonance angiography did not show occlusion of major intracranial arteries (D). Peripheral blood smear revealed mild fragmented red blood cells (RBCs, arrow head) and few platelets that indicated microangiopathic hemolytic anemia (E) on the first day. Forty-eight hours later, severe hemolysis with more fragmented RBCs (arrow) was followed (F).

**Table.** Series of patient's hematogram and disseminated intravascular coagulation profiles

| Variable  | Normal range    | On admission | Second day | Third day  |
|---|-----------------|--------------|------------|------------|
| White blood cell count (per mm <sup>3</sup> ) [band form %] | 3600-9600 [0-3] | 10200 [3]    | 13600 [10] | 18000 [16] |
| Hemoglobin (g/dl)/Hematocrit (%)                            | 12-16/33-47     | 10.6/31.8    | 8.3/23.8   | 6.9/18.5   |
| Platelet count (per mm <sup>3</sup> )                       | 120000-330000   | 6000         | 12000      | 11000      |
| Fibrinogen (mg/dl)  | 180-350         | 239.8        | 326.5      | 243.1      |
| D-dimer (ng/ml)   | 0-324           | 812          | 816        | 1299       |
| Activated partial thromboplastin time (seconds)             | 23.9-34.9       | 27.4         |            | 28.8       |
| Prothrombin time (seconds)                                  | 9.9-10.6        | 12.1         |            | 12.7       |

sion coefficient imagings (Fig. C), multiple lesions were seen over bilateral cerebral hemispheres and acute diffusely cerebral infarctions was impressed. However, no apparent intracranial artery stenosis was found on the magnetic resonance angiography (Fig. D).

The rechecked platelet count was 12,000/mm<sup>3</sup> in citrated tubes and excluded the possibility of pseudothrombocytopenia. The cause of thrombocytopenia was carefully evaluated with extensive laboratory workups as follows: fibrinogen 239 mg/dl (normal, 180-350), D-dimer 816 ng/mL (normal, 0-324), C-reactive protein 2.6 mg/dl (normal, 0.02-0.8), lactate dehydrogenase 2865 U/L (normal, 135-214) and reticulocyte count 3% (normal, 0.5-1.5). Haptoglobin was <10 mg/dl (normal, 30-200). Direct and indirect Coombs tests were negative. An initial peripheral blood smear (PBS) showed mild schistocytes (fragmented red blood cells, Fig. E) without polychromatic erythroblasts. The results of anti-cardiolipin and anti-lupus antibodies, and tumor markers, including CEA, CA 15-3, CA 125 and CA 19-9, were unremarkable. Abdominal sonography, and chest and abdominal computed tomography (CT) were normal. Bacterial cultures three days later revealed viridans streptococci from one urine sample, *Staphylococcus aureus* from a sputum sample, and no growth from a blood sample.

At the 16th hour of hospitalization, myocardial infarction was diagnosed by the abrupt onset of tachypnea with elevated cardiac enzymes (Troponin I: 21.77 ug/L, normal 0-0.04; creatinine kinase MB: 67 IU/L, normal 7-25) and ST segment elevation in the anterolateral leads on ECG. Transesophageal echocardiography showed diffuse hypokinesia of the ventricles, and absence of aortic dissection or intracardiac vegetation. Endotracheal intubation and aggressive intravenous levofloxacin (500 mg qd) were given in the intensive care unit for the critical condition and the possibility of severe systemic infection. The ECG monitor displayed atrial fibrillation thereafter. A follow-up PBS showed severe hemolysis (Fig. F). Daily follow-up of the complete blood count and disseminated intravascular coagulation (DIC) profile are shown in Table. Under the impression of TTP and possible systemic infection, two additional antibiotics, intravenous cefepime (1 g bid) and

metronidazole (500 mg q8h), were added. The patient also received plasmapheresis but her condition deteriorated and she died at the 50th hour of hospitalization. No autopsy was performed.

## DISCUSSION

Our patient presented with a rapidly deteriorating course of thrombocytopenia, renal insufficiency, hemolytic anemia and diffuse cerebral infarctions. The differential diagnosis may include fulminant DIC, sepsis, vasculitis, and antiphospholipid antibodies syndrome (APS)<sup>(3)</sup>. A normal DIC profile at the time of admission, and a negative result for anti-cardiolipin and anti-lupus antibodies made the diagnosis of DIC or APS less likely. Unremarkable cardiac echo, abdominal sonography, and chest and abdominal CT findings further excluded DIC or APS.

TTP still remains a clinical diagnosis of exclusion as the level of ADAMTS13 is not available clinically. Only 40% of patients have all five features during their illness<sup>(15)</sup>, so the diagnosis of TTP should not be dependent on the presence of the entire pentad of clinical conditions. In addition to exclusion of other causes, the presence of two or more schistocytes in a microscopic field with a magnification of 100, thrombocytopenia and elevated lactate dehydrogenase, should be sufficient to make the diagnosis<sup>(16)</sup>.

Our case demonstrates that TTP coexisting with infections of respiratory and urinary tracts is a complicated and life-threatening condition. TTP may arise in association with streptococcus infection as described in two previously reported cases<sup>(13,17)</sup>. In our case, we cannot definitively state that the bacterial infection was the underlying cause of TTP. However, this infection might accelerate the vicious cycle<sup>(14)</sup> and resulted in a fatal outcome.

The neuroradiological findings in TTP patients are diverse and may be reversible<sup>(18)</sup>. Although brain gray matter is affected more than white matter by platelet thrombi<sup>(19)</sup>, brain image study is not a diagnostic measure for TTP but is useful in assessing prognosis<sup>(18,20)</sup>. Brain MRI of our case revealed diffuse cortical infarctions,

which may be an indication of one poor prognostic index for fatal TTP. Moreover, the development of myocardial ischemia and arrhythmia, compatible with other case reports of fatal TTP, suggests that ischemic injury to the heart and conduction system is the most likely mechanism of death<sup>(5,21)</sup>.

The management of TTP-induced ischemic stroke depends on successful TTP therapy. The currently recommended treatment of TTP is plasma exchange with infusion of fresh frozen plasma, which is based on the hypothesis of replacing vWF-protease and removing antibodies against the protease<sup>(22,23)</sup>. Larger plasma replacement may produce a better response when treating TTP patients<sup>(24)</sup>. About 10%-30% of TTP patients are refractory to plasma exchange therapy<sup>(25)</sup>. Poor cardiac function and a rapidly progressive course of our patient limited the use of plasmapheresis with a larger plasma infusion. In conclusion, coexisting bacterial infection, cardiac dysfunction and diffuse cerebral infarction seemed to be poor prognostic factors for TTP patients.

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