Thrombotic Thrombocytopenic Purpura and Systemic Lupus Erythematosus: Distinct Entities or Overlapping Syndromes?

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Citation

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Abstract

Thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) are distinct entities that share many overlapping features. The two diseases rarely coexist. To date, only twelve patients have had simultaneous presentations of TTP and SLE documented in the English literature. The current report describes the first case of such an occurrence in an elderly gentleman, followed by a brief review of the literature.

CASE

A 61-year-old man was transferred from a community hospital to a tertiary care centre for investigation and management of new onset of generalized tonic-clonic seizures and a 5-day history of confusion and malaise. He had no headaches or neck stiffness, and denied any cardiopulmonary, gastrointestinal, or constitutional symptoms. Past medical history was significant for porphyria cutanea tarda that had been well controlled by phlebotomies for the last 20 years. There was no history of recent head trauma and no known liver or kidney disease. He was a social drinker and ex-smoker. He was not on any regular medications prior to presentation.

On examination, the patient was very agitated, confused and disoriented, and febrile (38.5°C). He had mild jaundice and bilateral scleral icterus. A new grade II/VI systolic murmur was noted along the left sternal border. The remainder of the precordial, respiratory, and abdominal examination was benign. Petechiae and several ecchymoses were present on the extremities. There were otherwise no focal neurologic findings.

Investigations revealed microangiopathic hemolytic anemia, with a hemoglobin level of 77 g/L, total bilirubin of 130 umol/L, LDH of 1000, and 6 schistocytes/hpf on peripheral blood smear. Platelet count was decreased at 8 x 10^9/L. A direct antiglobulin (Coomb's) test was reported as weakly positive. Results of other preliminary investigations including white blood cell count, renal and liver function tests, coagulation profiles, and urinalysis were normal. A head CT scan did not demonstrate any intracranial abnormalities to account for the patient's seizures. The patient was started on heparin for DVT prophylaxis and phenytoin for secondary seizure prevention.

The constellation of microangiopathic hemolytic anemia, thrombocytopenia, seizures, and pyrexia suggested a diagnosis of thrombotic thrombocytopenic purpura (TTP), so plasma exchange (PLEX) was promptly implemented. Initial response was favourable such that by the 5th day of PLEX, the patient's confusion had improved, jaundice had diminished, and platelet count had stabilized at 65 x 10^9/L. Surprisingly, this response was transient and the platelet count unexpectedly declined over the next week to 13 x 10^9/L despite ongoing therapy with PLEX.

A heparin-induced thrombocytopenia (HIT) assay and repeat blood cultures were negative. A bone marrow aspiration and biopsy showed only erythroid hyperplasia. Interestingly, tests of the patient's autoantibody profile showed ANA in 1:640 titre, and strongly positive anti-Ro and anti-La antibodies, consistent with systemic lupus erythematosus (SLE). Tests for anti-dsDNA, anti-Smith antibodies, and the remaining extractable nuclear antigens were negative. Anti-phospholipid antibodies were absent. A subsequent brain MRI scan demonstrated multiple areas of small infarcts involving the occipital lobes and cerebellum, which are features seen in CNS vasculitis.

The patient was promptly started on cyclophosphamide and high-dose steroids for his new diagnosis while PLEX was discontinued. On the new therapy, his platelet count improved steadily to 147 x 10^9/L within one week. Seizures did not recur. He was discharged home with prednisone and instructions to follow-up at the rheumatology clinic.

DISCUSSION

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening syndrome characterized by the classic pentad of clinical features that includes microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction. There is a female predominance of 3:2 and the median age at diagnosis is 35 years.[1] A closely related disorder called hemolytic uremic syndrome (HUS) shares similar features with TTP, but it is more common among children and renal deficits tend to be more severe.[2]

Infections, malignancies, medications, and autoimmune diseases are known to precipitate TTP (refer to Box 1), but the precise pathophysiology of this disorder remains inconclusive. Patients with TTP have a deficiency in a specific protease, named ADAMTS-13, which normally degrades large von Willebrand factor (vWF) multimers into smaller forms in the peripheral circulation.[3] The accumulation of unusually large vWF multimers in TTP promotes abnormal platelet aggregation, resulting in microvascular thrombi and occlusions that may affect numerous organs.[4] Peripheral blood, central nervous system, and renal involvement are most common.

Accurate and timely diagnosis of TTP is important because mortality is high without prompt therapy. However, diagnosis can be challenging because patients with early disease seldom present with the classic pentad. If clinical suspicion exists, unexplained thrombocytopenia and microangiopathic hemolytic anemia are sufficient for diagnosis. To further complicate the diagnostic dilemma, TTP also shares many similar characteristics with systemic lupus erythematosus (SLE) (refer to Box 2).

SLE is an autoimmune disorder characterized by chronic inflammation and production of antinuclear antibodies. Like TTP, patients with SLE may present with hemolytic anemia, thrombocytopenia, neurologic deficits, fever, and renal insufficiency. The finding of fragmented RBC's, or schistocytes, favours the diagnosis of TTP. Because treatment of these two diseases is different, distinguishing between the diagnoses is essential to ensure optimal clinical outcome. Therapy mainly consists of plasma exchange (PLEX) in TTP and corticosteroids and immunosuppressants in SLE.

Interestingly, TTP has been infrequently described to occur in SLE patients. A review of the English literature revealed only 58 patients to date who have been affected with both diseases.[1,5,6] In most settings, patients had pre-existing SLE prior to developing TTP. The overall mortality in cases of co-existing diseases after treatment was 33%, which is higher than either disease alone.[5]

Very rarely, TTP may present simultaneously with SLE, such as the patient in this report. Twelve cases of simultaneous presentation of TTP and SLE have been documented to date.[5] Most of the patients were females (75%) and ranged in age from 12 to 46 years.[5] This is the first case of simultaneous presentation of TTP and SLE in a male above 60 years of age.

In the current case, PLEX was appropriately initiated for TTP due to evidence of microangiopathy and most features of the classic pentad. The initial response to PLEX supported the diagnosis. Additional investigations were subsequently required to consider concurrent processes, other than TTP, that may account for the patient's refractory thrombocytopenia to ongoing PLEX therapy. The patient's autoantibody profile in association with evidence of CNS vasculitis and autoimmune hemolytic anemia (positive Coomb's test) soon confirmed that he also had SLE. He was started on prednisone and cyclophosphamide thereafter with good response.

TTP and SLE share many overlapping features, but the presence of microangiopathy is more characteristic of TTP. The precise clinical relationship between the two disorders remains poorly defined. Recent studies have suggested that autoantibodies and ADAMTS13 deficiency are involved in the pathogenesis of both TTP and SLE to varying degrees, leading some to speculate that the two conditions are more closely associated than currently believed.[7,8]

In summary, three key clinical lessons can be derived from this case. First, a high clinical suspicion for TTP and SLE is warranted in patients of all ages who present with hemolysis, low platelets, fever, and neurologic and renal deficits. Second, although rare, TTP and SLE can present and occur simultaneously. Finally, until the mechanisms of disease are better elucidated, it is paramount to distinguish whether the

patient has TTP, SLE, or both because there are serious implications for treatment and prognosis.

Figure 1

Box 1: Precipitants of Thrombotic Thrombocytopenic Purpura (TTP)

Idiopathic
Medications
· chemotherapy (mitomycin, bleomycin, cisplatin, gemcitabine)
· immunosuppressants (cyclosporine, tacrolimus)
· others (quinine, ticlopidine, clopidogrel, valacyclovir, oral contraceptives)
Infections
· HIV and AIDS
· enterohemorrhagic E.coli (typically E.coli O157:H7)
Malignancies
· carcinomas of the breast, GI tract, pancreas, and prostate
Autoimmune Diseases
· antiphospholipid antibody syndrome
· systemic lupus erythematosus
· scleroderma
Pregnancy or Post-partum

Figure 2

Box 2: Comparison of Clinical Features in TTP versus SLE

Thrombotic Thrombocytopenic Purpura
· hemolytic anemia* (microangiopathic, eg. schistocytes)†
· thrombocytopenia*
· neurologic deficits*
· renal insufficiency*
· fever*

Systemic Lupus Erythematosus
· hemolytic anemia* (autoimmune, eg. positive Coomb's test)†
· thrombocytopenia*
· neurologic deficits*
· renal insufficiency*
· fever*
· photosensitivity
· malar or discoid rash
· oral ulcers
· serositis
· arthritis
· positive ANA or anti-dsDNA titres

** denotes overlapping features*
† evidence of microangiopathy favours the diagnosis of TTP while evidence of an autoimmune process suggests SLE

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