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Thrombotic Thrombocytopenic Purpura in the Setting of Systemic Sclerosis

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OBJECTIVES To describe the association between thrombotic thrombocytopenic purpura (TTP) and systemic sclerosis (SSc) and the methods to distinguish TTP from scleroderma renal crisis (SRC).

METHODS A case of TTP that developed in a patient with preexisting SSc is described. Medline/PubMed was searched for literature pertaining to an association between TTP and SSc, with special attention given to distinguishing TTP from SRC. In addition, the role of von Willebrand cleaving protease in the pathogenesis of TTP is reviewed.

RESULTS Including the present case, there have been 9 reports of TTP in association with SSc in the literature. In the majority of these cases TTP presented with features compatible with SRC such as renal dysfunction, thrombocytopenia, hypertension, and microangiopathic hemolytic anemia. Von Willebrand cleaving protease activity is depressed in patients with acute TTP.

CONCLUSIONS TTP in association with SSc has been reported rarely. The diagnosis of TTP, and the distinction from SRC, may be challenging, as these cases may resemble SRC. However, the correct diagnosis is critical because treatment differs substantially for each of these life-threatening conditions. Currently, the assessment of von Willebrand factor cleaving protease activity may assist in making this distinction.

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KEYWORDS thrombotic thrombocytopenic purpura, scleroderma renal crisis, systemic sclerosis, von Willebrand cleaving protease, thrombotic microangiopathy

Thrombotic thrombocytopenic purpura (TTP), originally described by Moschcowitz in 1924, is a rare syndrome characterized by a pentad of acute renal impairment, thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurologic abnormalities, and fever (1). The signs and symptoms of TTP result from microvascular platelet clumping (2,3). Pathological specimens reveal "thrombotic microangiopathy" in the kidneys, cerebral vasculature, skin, and other affected organs. The incidence of TTP in the United States has been estimated to be 3.7 cases/million (4). Untreated TTP is often rapidly fatal, whereas current plasmapheresis-based therapy may be lifesaving (5,6). TTP has a well-established association with systemic lupus erythematosus (7-22), whereas there have only been a few reports of the coexistence with systemic sclerosis (SSc). When TTP occurs in the presence of SSc, it may mimic scleroderma renal crisis (SRC). As the treatment of TTP is different from that of SRC, failure to make the correct diagnosis may delay life-saving therapy. Here, we present a case of TTP occurring in a patient with SSc and we review the literature concerning the association and diagnostic strategies to distinguish the 2 conditions.

Methods

A patient with longstanding limited SSc who presented with TTP is described and the clinical, laboratory, and radiological findings of the patient are reported. Medline/PubMed for the years 1966 to 2003 was searched for an association of TTP and SSc using the keywords "systemic sclerosis," "scleroderma," "thrombotic thrombocytopenia purpura," and "thrombotic microangiopathy." In addition, special attention was given to distinguishing TTP from

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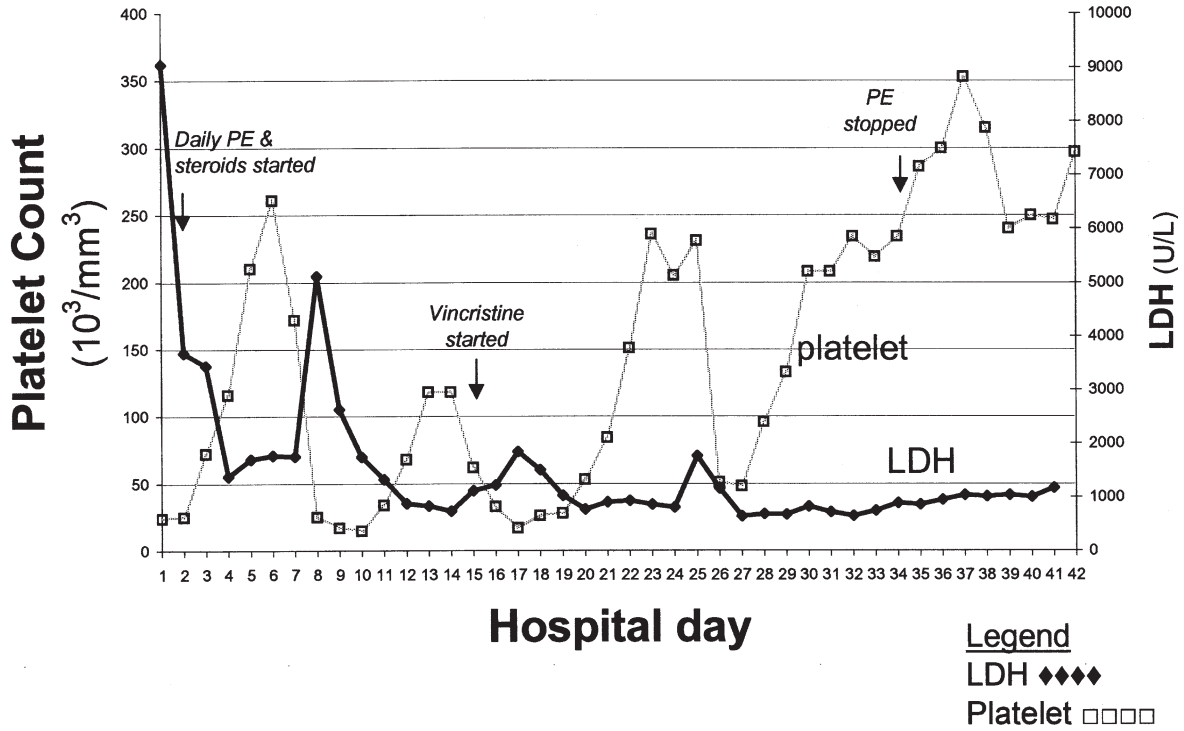

Figure 1 Graph of LDH and platelet count of TTP-SSC case in relation to therapy. Abbreviations. PE, plasmapheresis; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

SRC. Thus, an additional search was performed using the keywords "scleroderma renal crisis." We also briefly review the role of von Willebrand cleaving protease in the pathogenesis of TTP.

Results

Case Reports

A 22-year-old African American woman with a 4-year history of SSc according to the American College of Rheumatology (ACR) criteria for SSc (23) was brought to the emergency department by her mother for altered mental status; she was reportedly speaking to God. The patient reported headaches, fatigue, pleuritic chest pain, hemoptysis, and epistaxis. Her clinical features of SSc included distal skin tightening, myositis, Raynaud's phenomenon, alveolitis, pulmonary hypertension, gastroesophageal reflux, antinuclear antibody titer of 1:1280, and a positive Scl-70 antibody. Surgical history included bilateral digital sympathectomies for Raynaud's phenomenon. At presentation, medications were lansoprazole and prednisone 7.5 mg/day; she had previously received d-penicillamine for skin tightening and cyclophosphamide for alveolitis.

Physical examination revealed a temperature of 38.5°C, blood pressure (BP) 153/88 mm Hg, pulse of 132/min, and respiratory rate 22/min. The patient was obese and in no apparent distress. Cardiopulmonary examination was significant only for tachycardia. The abdomen was soft with mild tenderness and normal bowel sounds. The skin revealed ecchymoses on the anterior chest and lower extremities, tightened skin of the hands and face, and hyperpigmentation of the dorsal surfaces of the hands. She was occasionally inappropriate but there were no focal neurological deficits and she was fully oriented.

Initial laboratory evaluation included a white blood cell count of 13,100/μL, hemoglobin 7.2 g/dL, platelets 9000/mm^3 (see Fig 1), serum creatinine 0.7 mg/dL, total bilirubin 2.6 mg/dL, direct bilirubin 1.3 mg/dL (normal 0.0-0.4), lactate dehydrogenase (LDH) 9049 U/L (normal 200-650), haptoglobin 7 mg/dL (normal 31-167), and a reticulocyte percent of 14.7% (normal 0.4-1.8%). The peripheral smear revealed schistocytes. Urinalysis revealed specific gravity 1.017, 1 WBC per high power field (HPF), 0 RBC/HPF, negative nitrates, and negative leukocyte esterase. CSF obtained by lumbar puncture had 3 WBCs/μL, 5 RBC/mL, protein 68 mg/dL, and glucose of 47mg/dL. Complement components, prothrombin time, and activated partial thromboplastin time were normal. Chest x-ray revealed cardiomegaly and blunting of the left costophrenic angle. Computerized tomography of the brain was normal. Transthoracic echocardiogram revealed a moderate-sized pericardial effusion. A provisional diagnosis of TTP was made based on the presence of fever, mental status changes, thrombocytopenia, and MAHA. Von Willebrand factor (vWF)-cleaving protease was measured on hospital day 1 and was 0% (clinical activity with normal range between 28 and 119%). Her TTP was treated with a complex regimen including glucocorticoids, plasmapheresis, and vincristine. Plasmapheresis was initiated within the first 36 hours of hospitalization and was continued daily for a total of 32 treatments. She was initially treated with methyl-