Thrombotic Thrombocytopenic Purpura: Report of a Case With Possible Immune Etiology

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Thrombotic thrombocytopenic purpura (TTP) is a disorder of unknown etiology. An immunologic basis has been suggested, although proof is lacking. The immunologic, hematologic, and autopsy findings in a case of TTP occurring 6 wk postpartum are described. Immunofluorescent studies revealed the presence of IgM and complement, as well as fibrin in the vicinity of the endothelium and in thrombi in small blood vessels in multiple organs. These findings suggest an active immunologic process in this case. While TTP is probably of diverse etiology, confirmation of these findings in further cases would provide a rational basis for the use of immunosuppressive therapy.

The first case of thrombotic thrombocytopenic purpura (TTP) was described by Moschcowitz in 1925. Since then, over 300 cases have been reported. In this article we describe the immunologic, hematologic, and autopsy changes observed in a case of TTP and provide evidence that at least in some cases an immunologic process may be responsible.

CASE REPORT

A 22-yr-old woman was admitted to the Alfred Hospital in March 1971 6 wk after a normal delivery and an uncomplicated pregnancy. Three wk after delivery, symptoms of lethargy, anorexia, dizziness, and headache developed, accompanied by spontaneous bruising, a transient episode of blurred vision, and dark urine. On admission to another hospital, physical examination revealed pallor and generalized purpura, but no fever. Macroscopic hematuria was found, but there was no menstrual bleeding. The hemoglobin was 7.0 g/100 ml, WBC 13,300/cu mm with a neutrophilia, and platelets less than 10,000/cu mm. Reticulocytes were 31%, and a blood film showed anisocytosis and poikilocytosis with seven normoblasts per 100 WBC. A tourniquet test was positive. Bone marrow examination showed erythroid hyperplasia and increased megakaryocytes, which were mainly immature forms. Three LE-cell preparations and a Coombs' test were negative. Treatment with penicillin, blood transfusions, and prednisone (60 mg/daily) was commenced. There was deterioration in her condition with bleeding from the gums and a further transient episode of blurred vision, and she was transferred to the Alfred Hospital. During transfer a transient left-sided sensory disturbance occurred.

On arrival, physical examination revealed pallor, mild icterus, loin tenderness, ecchymoses on all limbs, hemorrhagic tonsils, petechiae on palate and fauces, and a Roth's spot.
in the right fundus. The temperature was 38°C. The liver was palpable 2 cm below the costal margin, but there was no splenomegaly, lymphadenopathy, or arthritis. She was alert and without neurologic signs apart from a variable depression of deep tendon reflexes on the left side. The dose of prednisone was doubled to 120 mg/day, and further therapy was deferred pending confirmatory evidence for the clinical diagnosis of TTP. Four hours after admission, her condition deteriorated abruptly with intermittent confusion and dysphasia and she rapidly lapsed into coma and died.

**Investigations**

The hemoglobin was 9.0 g/100 ml, WBC 13,000/cu mm with a neutrophilia, and platelets 1000/cu mm. A blood film showed marked anisocytosis and poikilocytosis with many fragmented erythrocytes, a few microspherocytes and nucleated red cells, and marked polychromasia. Reticulocytes were 15%. The partial thromboplastin time, prothrombin time, and clotting time were normal, although clot retraction was impaired. Fibrinogen was 230 mg/100 ml. The thrombin time was prolonged at 22 sec (control, 16 sec) as was the skin bleeding time at 12 min (Ivy). Fibrin-split products were 154 μg/ml. (Normal, < 10 μg/ml). There was no hemoglobinemia. There was macroscopic hematuria but no hemoglobinuria. Blood urea was 105 mg/100 ml, and there was a mild metabolic acidosis.

**Autopsy Findings**

At autopsy, mild jaundice and generalized skin purpura were present. There were numerous hemorrhagic foci in the myocardium, and microscopically small vessels were variably occluded by thrombi (Fig. 1), some being associated with necrosis of muscle and a moderate leukocyte infiltrate, while others were associated with extensive interstitial hemorrhage. Kidney size was normal, but the surfaces showed tiny pitted scars and there
were punctate hemorrhages throughout the parenchyma. Focal glomerular lesions were present in which one or more capillary loops were occluded by eosinophilic material with staining characteristics of fibrin, which was sometimes in continuity with similar material in the lumen of the afferent arteriole (Fig. 2). Endothelial swelling and fibrin deposition was observed within the walls of the arterioles. Localized areas of tuft capillary wall necrosis were present. There were several areas of infarction with early organization associated with occlusion of the interlobular arteries. Areas of tubular atrophy were seen, and many proximal tubular cells contained granular material with the staining characteristics of fibrin. Examination of the brain showed widely scattered tiny punctate hemorrhages with a densely grouped collection in the midbrain. Microscopically small vessels were variably occluded by fibrin thrombi, with fibrin deposition within their wall and leakage into surrounding tissue. Similar vascular lesions with variable hemorrhage and parenchymatous necrosis were present in the spleen, lymph nodes, pancreas, liver, and small intestine.

**Immunologic Studies**

Immunoglobulin levels with serum taken prior to death were measured by radial immunodiffusion and were within normal limits (IgA, 160 mg/100 ml; IgG, 940 mg/100 ml; IgM, 120 mg/100 ml). Routine immunofluorescence tests for autoantibodies in the patient’s sera, using the “sandwich” method and a fluorescein isothiocyanate conjugated goat-anti-human globulin were all negative and included antinuclear factor.

Cryostat sections of tissues taken at autopsy and frozen in liquid nitrogen isopentane slurry were stained by the following monospecific fluorescein conjugated antisera: anti-albumin, antifibrinogen, anticomplement (FCC), anti-IgM, anti-IgG, and anti-IgA. An anti-human platelet antibody absorbed with normal human gastrointestinal tract mucosa was also used.
Fig. 5. Patient's myocardium stained with anticomplement to show staining of the endothelial aspects of blood vessels. X 215.

Fig. 6. Blood vessels stained with anti-IgM to show partial occlusion and staining of vessel wall. X 300.

There was marked focal staining of kidney glomeruli and in some cases of the afferent blood vessels with both anti-IgM and anticomplement sera (Figs. 3 and 4). There was also a moderate amount of staining with antifibrinogen. There was no glomerular staining with anti-IgG or with other antisera. Blood vessels in the myocardium, brain, and spleen, but not in liver and lung, gave a similar staining pattern (Figs. 5 and 6). Blocking experiments with unlabeled antifibrinogen confirmed the specificity of both anti-IgM and anticomplement. Positive staining with antifibrinogen, anti-IgM, and anticomplement was present in both thrombi and in the vicinity of the endothelium.

When sections of normal tissues were tested by an indirect immunofluorescence technique using the patient's serum and a fluorescein-conjugated goat-antihuman globulin, there was no specific binding detected.

DISCUSSION

The case reported here showed the classic clinical pentad of pyrexia, anemia, neurologic symptoms and signs, thrombocytopenic purpura, and renal abnormalities of TTP. Autopsy findings were also typical. These clinical and pathologic features, together with the negative LE preparations and antinuclear factor make it extremely unlikely that this was a case of systemic lupus erythematosus. This case is of importance because of the strong evidence that an immunologic mechanism may have been responsible for the disorder.

The pathogenesis of TTP is unknown and has been the subject of considerable speculation and recent review. Controversy has centered mainly on whether the disease is one of primary intravascular coagulation or of primary vessel wall damage with secondary thrombosis. Coagulation studies and histol-
ogy cannot distinguish these with certainty. Although it has been suggested that TTP may be a human counterpart of the generalized Shwartzman reaction\textsuperscript{6,7} with primary intravascular thrombosis, the widespread nature of the fibrin thrombi and the occasional favorable response to corticosteroids fail to support this concept. Primary vessel wall damage is currently thought to be more likely and is supported by the finding of presumptively prethrombotic subendothelial lesions\textsuperscript{8,9} and aneurysmal dilatation at arteriolar-capillary junctions.\textsuperscript{10} A popular theory proposes that the damage is immunologic in nature,\textsuperscript{11} but direct proof is lacking, although autopsy studies have recorded similarities to systemic lupus erythematosus,\textsuperscript{12} and the two diseases may coexist.\textsuperscript{13,14}

The findings in the present case support an immunologic basis since complement was present in the lesions and IgM was the only immunoglobulin found. Similar techniques applied in a previous case yielded negative results\textsuperscript{9} suggesting that the disease may have more than one pathogenetic mechanism. Positive immunofluorescence with fibrinogen and negative immunofluorescence with platelet antisera are consistent with previous reports\textsuperscript{9,15} suggesting that the thrombi are largely composed of fibrin.

The treatment of TTP has been unsatisfactory, and the disease continues to have a high mortality.\textsuperscript{5} Exchange transfusion,\textsuperscript{16} corticosteroids,\textsuperscript{17} heparin,\textsuperscript{18-19} magnesium sulfate,\textsuperscript{20} streptokinase,\textsuperscript{21} antimetabolites,\textsuperscript{22} and splenectomy\textsuperscript{23,24} have been used with occasional success, and their status has been recently reviewed.\textsuperscript{5} At present a combination of corticosteroids and splenectomy has proved most successful,\textsuperscript{25} although in view of the pathology, heparin has a more rational basis. The use of immunosuppressants other than corticosteroids has not been widely reported and has not proved successful.\textsuperscript{25-28,27} However, the patients treated were at a near-terminal stage of their illness. If our findings are confirmed in other cases, further investigation of the use of immunosuppressive therapy is indicated, particularly in view of the continued high mortality of this disorder. Such therapy would probably require time to be effective and should probably be combined with the currently successful forms of treatment. It may be most useful in the less rapidly progressive forms of the disease or following temporary remission induced by other treatment.

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