Thrombotic Thrombocytopenic Purpura and Systemic Lupus Erythematosus

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ALTHOUGH some investigators have noted an occasional association of thrombotic thrombocytopenia purpura (TTP) with systemic lupus erythematosus (SLE), the literature contains many reports denying the existence of any clinical or pathologic relationship between these entities. Levine and Stearn[11] reported both conditions present at the time of death in 23 per cent of a series of cases they reviewed.

In the case here reported, changes compatible with SLE from both the clinical and pathologic standpoints were found to be present with lesions of TTP occurring as a terminal episode.

Report of a Case

A 39-year-old white housewife dated the onset of illness at age 17 when painful swelling of the left shoulder and right knee developed. At age 36 she had a recurrence involving fingers, wrists and ankles. Pleurisy on the left side also developed, and subsequently pleural effusion. A high dosage of salicylates was prescribed at that time. Two years later, at age 38, arthritis recurred shortly after a complete hysterectomy. Despite salicylates, the symptoms became more severe. Results of tests for rheumatoid arthritis and lupus erythematosus were negative. The erythrocyte sedimentation rate was increased. Use of salicylates was discontinued and chloroquine begun. The arthritic activity increased, with painful swellings of hands, wrists, left elbow and right knee. Pleurisy developed on the left side and an erythematous rash appeared on the malar areas. Three months later the patient was put in hospital because of an exacerbation of the joint and chest sypmtoms.

On physical examination the blood pressure was 180/90 mm of mercury, the pulse 90 per minute and regular, respirations 18 per minute and temperature 98.6°F. Crepitant rales were noted in the left lung base. A grade II to VI systolic murmur was heard at the apex and a grade II to VI diastolic murmur over the left sternal border. The hemoglobin was 10.8 gm per 100 ml, the hematocrit 34 per cent. Leukocytes numbered 5200 per cu mm with a shift to the left of the neutrophils in the cell differential. Platelets were adequate. The reaction for albumin in the urine was three to four plus and on microscopic examination hematuria was noted. An electrocardiogram was interpreted as showing ventricular hypertrophy with eschemia and/or strain.

Prednisolone, 20 mg a day, and hydrodiuril, 50 mg a day, were given. The status of the patient remained unchanged for 72 hours except for a seven pound loss in weight and a decrease in chest pain. Blood urea nitrogen was 23 mg per 100 ml with an increase of serum creatinine to 1.8 mg per 100 ml. By the seventh hospital day, left pleural effusion developed. Two tests for lupus erythematosus were negative. Reaction to a direct Coombs test was weakly positive. Serum proteins were 7.6 gm per 100 ml, with albumin of 3.9 gm and globulin of 3.7 gm. A blood culture was negative and the antistreptolysin-O titer normal. When examined again on the fifteenth hospital day the urine was strongly reactive for albumin and there were 100 to 150 leukocytes and 50 to 60 erythrocytes per high power field. The blood urea nitrogen was 45 mg per 100 ml. Leukocytes numbered 16,300 per cu mm with a left shift. The patient was digitalized. On the nineteenth hospital day, serum potassium was 2.9 mEq per 1 and supplemental potassium therapy was begun. On the twenty-first hospital day, the patient complained of dyspnea, nausea and chest pain and there were episodes of vomiting and hemoptysis. A day later a generalized hemorrhagic rash suddenly appeared. At this time platelets numbered 46,000 per cu mm of blood, blood urea nitrogen was 102 mg per 100 ml and serum electrolytes were within normal range. The hemoglobin was 9.8 gm per 100 ml and the hematocrit was 33 per cent. Leukocytes numbered 15,000 per cu mm with a persistent left shift. On the twenty-third hospital day, the patient became mentally dull and was incontinent. Crepitant rales developed in the chest. Generalized convulsions occurred and calcium gluconate was given. By the twenty-fifth hospital day, the blood urea nitrogen was 114 mg per 100 ml, serum potassium 5.7 mEq and chlorides 91 mEq per liter. The patient's condition steadily deteriorated, urinary output decreasing, and she died on the twenty-sixth hospital day.

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Pathologic Findings

On postmortem examination, fibrous adhesions were seen on serous surfaces of the body. There were fibrinous adhesions on the pericardium and petechiae on the epicardium. The heart weighed 525 grams with the left ventricular segment weighing 350 grams. Small granular and friable vegetations were seen on the ventricular aspects of two cusps of the aortic valve. On histologic examination of aortic valve an atypical verrucous lesion free of inflammation or bacteria was seen. Fibrinoid necrosis, fibrin thrombi and inflammation of vessel walls were present in the coronary arteries (Figure 1). Fibrinoid necrosis was seen in arterioles of splenic, hepatic and adrenal vessels, some with aneurysmal dilation. Fibrin thrombi were observed in these vessels, some of them appearing to be free within the lumen and some attached to the vessel walls. The kidneys together weighed 300 gm. The surfaces of the kidneys were hemorrhagic and on section there

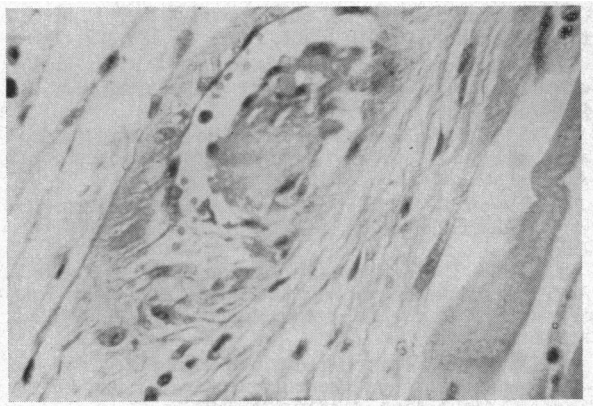

Figure 1.—Fibrin thrombus adherent to the wall of a small blood vessel in the myocardium. Hematoxylin and eosin stain, ×450.

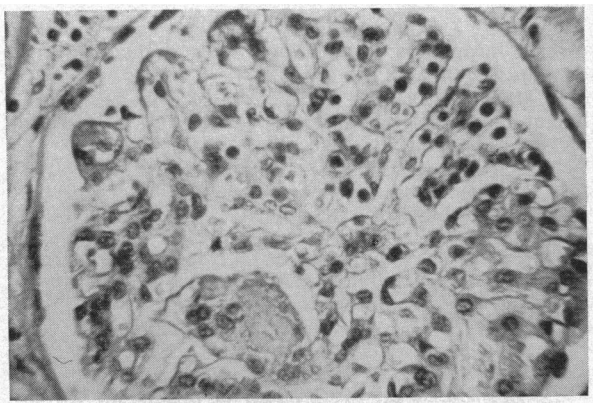

Figure 2.—Fibrinoid necrosis of arterioles of a glomerulus with basement membrane proliferation. Hyaline thrombi are present in the glomerulus. Hematoxylin and eosin stain, ×1,000.

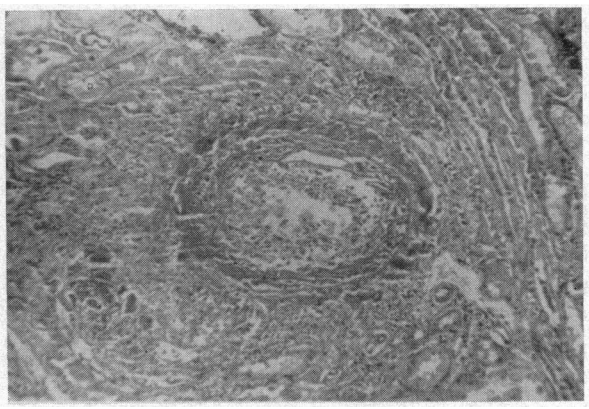

Figure 3.—Medium-sized renal artery involved in acute inflammation. Endothelial proliferation and necrosis is present. Hematoxylin and eosin stain, ×125.

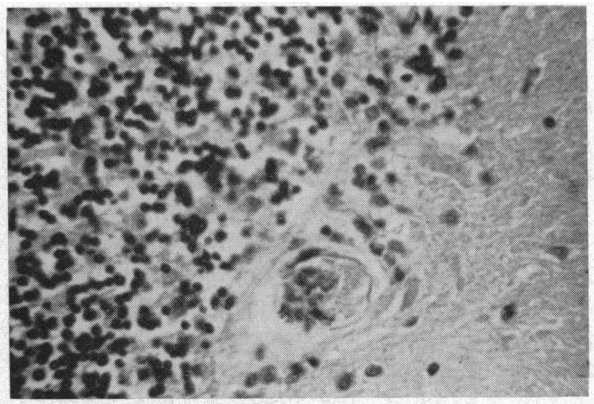

Figure 4.—Fibrin thrombi present in a cerebellar arteriole. Hematoxylin and eosin stain, ×125.

were both old and new areas of infarction, with recent petechial and confluent hemorrhages as well. Microscopically, many of the glomeruli showed proliferation of the basement membrane with hyalinization resulting in "wire-loop" glomeruli in which fibrinoid necrosis had occurred (Figure 2). Hyaline thrombi were noted in the glomeruli. Both small and medium-sized arteries were involved (Figure 3). Petechiae were seen in the putamen, pons, medulla and cerebellum. There were fibrin thrombi in the meningeal, cerebral and cerebellar vessels (Figure 4). The bone marrow was hypercellular and megakaryocytes were increased. Fibrinoid necrosis and fibrin thrombi were present in the vessels of adipose tissue and skin. Histologic sections of skin revealed atrophy of the epidermis, with increase in collagen fibers, some areas of which had undergone fibrinoid necrosis.

Comment

In this case the renal, splenic, endocardial and cardiovascular changes frequently associated with

systemic lupus erythematosus[10] were present, as were the manifestations of TTP, including intraluminal hyaline masses, endothelial proliferation and aneurysmal dilatation of small vessels.[8,13,14]

The thrombocytopenia found in TTP is a constant feature and is usually severe, resulting in petechial hemorrhages in the skin, mucous membranes and viscera.[12] Characteristically, this low platelet count is refractory to therapy. Hirsh and Gardner[9] reported that the survival time of transfused normal platelets in these patients is reduced. This observation, considered with the fact that bone marrow megakaryocytes were present in adequate number, leads to the conclusion that the thrombocytopenia is the result of peripheral platelet destruction. However, Craig and Gitlin,[3] using fluorescent techniques, were unable to demonstrate platelet components in these thrombi. They found that the thrombi consisted largely of fibrin. Using several tincturing methods, Fisher and Creed[7] concluded that the blood vessel change in TTP was fibrinoid degeneration which resulted in subendothelial accumulation of eosinophilic periodic acid Schiff-positive material. This substance is thought to be a precipitate of mucopolysaccharide with a protein,[2] the source of which is vascular endothelium.[4] It appears, then, that the primary lesion in TTP is vascular. The altered surface of vessels leads to the formation of thrombi that contain fibrin.[8] Partial occlusion of these small vessels results in traumatic destruction of both erythrocytes and platelets, leading to both the anemia and thrombocytopenia found in this disease.[13] The hemolytic anemia varies in its severity in TTP, and the direct Coombs test is almost invariably negative. However, in a few cases, such as the one here presented, the result of the test is positive.

This observation suggests that hemolysis is not caused by an antibody as in hemolytic anemia of the auto-immune type,[5] but possibly by an antibody present in the blood but not detected by the usual Coombs test reagent.[6]

Pathologic changes present in this case were consistent with SLE. The blood vessel alterations were not unlike those of that disease, although the larger blood vessel lesions noted in the present case are not as common in SLE. The vascular lesions present were those of the microangiopathic necrotidides described by Dacie[5] and Alarcon-Segovia and Brown.[1]

The observations made by Levine and Stearn[11] that the group of patients with TTP who manifest clinical evidence of SLE constitutes a subgroup within the total number of patients with TTP seem to apply in this case. If it is assumed that these patients have SLE, it may be safe to say that the immunologic and vascular alterations that take place in them may form an internal environment conducive to the development of TTP as a terminal event. This concept is supported by clinical and laboratory findings in the present case that were consistent with SLE followed by a fulminating terminal picture of TTP.

Summary

A case report is presented of systemic lupus erythematosus with late manifestations of thrombotic thrombocytopenic purpura. A brief discussion of the etiologic factors of these disease entities is also presented.

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