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Thrombotic Thrombocytopenic Purpura-like Syndrome Associated with Systemic Lupus Erythematosus

— Combined Treatment with Plasmapheresis and Fresh Frozen Plasma Infusion —

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We report on a patient with systemic lupus erythematosus, who, during the course of the illness, developed thrombotic thrombocytopenic purpura. In this case, the coexistence of these two conditions was confirmed by laboratory and pathologic findings. The infusion of fresh frozen plasma with plasmapheresis reversed the course of thrombotic thrombocytopenic purpura.

Key Words: *Systemic lupus erythematosus, Thrombotic thrombocytopenic purpura, Plasmapheresis, Infusion of fresh frozen plasma*

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a somewhat rare clinical syndrome characterized by pentad of fever, thrombocytopenic purpura, microangiopathic hemolytic anemia, renal involvement, and fluctuating neurologic abnormalities, which is recognized with increasing frequency so that more than 400 cases have been reported to date.

Systemic lupus erythromatosus (SLE) is a clinical syndrome of unknown etiology in which tissues and cells are damaged by deposition of pathogenic autoantibodies and immune complexes and by complement activation. Clinically evident thrombotic complications occur in 9% to 12% of patients with SLE (Peck et al., 1978) and TTP shares many clinical features with SLE. While the many cases and studies of either disease have been reported, only rarely have both syndromes been clearly documented in individual patients (Ridolfi and Bell, 1981).

We have recently treated a patient with well documented SLE who showed a clinical presentaion of TTP. The thrombotic microangiopathy of TTP was documented by gum biopsy. The clincal thrombocytopenic and thrombotic complication of TTP were reversed by repeated fresh frozen plasma infusion with plasmaphresis.

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CASE REPORT

A 24-year-old man was admitted because of fever, headache, facial and leg edema accompanied by multiple arthralgia. He had been relatively well until 3 months before admission, when the fever, headache, generalized edema and purpura on both legs developed. He had no specific past medical history but his brother had died of lung cancer.

On examination, blood pressure we 180/90 mmHg, heart rate was 90/min, respiration rate 20/min and temperature 37.2°C. There was an erythematous rash on the malar region and several aphthous ulcers at the oral cavity. The head and neck were normal. the conjunctivae were slightly anemic, the sclerae were anicteric. The lungs were clear and the heart sound was regular without murmur. Abdominal examination disclosed on hepatosplenomegaly. Mild pitting edema was observed. Neurologic examination was negative.

The urinalysis revealed proteinuria, 1 to 3 WBC and many red blood cells per high power field. The amount of protein excretion for 24 hours was 9.23g. the hematocrit was 21.3%; and the hemoglobin 7.6 g/dl. The WBC was 1,800/mm^3, with neutrophil 52% and lymphocyte 42%. The platelet count was

91,000/mm^3. MCV was 87.2 fl, MCH 31.9 pg, MCHC 36.6%. Peripheral blood smear showed normal red cell morphology and mild thrombocytopenia. The fasting blood sugar was 86mg/dl, the urea nitrogen 28mg/dl, the creatinine 1.4mg/dl, the total protein was 4.3g/dl and the albumin was 1.7g/dl. The sodium was 138mEq/L, the potassium 5.2mEq/L, the calcium 7.9mg/dl, the phosphate 5.3mg/dl and the chloride was 115mEq/L. The total bilirubin was 0.4 mg/dl and direct bilirubin was 0.1 mg/dl. The serum aspartate aminotransferase was 27 units, the serum alanine aminotransferase 17 units, LDH 308 units with normal fraction distribution and the alkaline phospatase was 5.4 KA/dl. The serum iron was 40 ug/dl, the total iron binding capacity 194 ug/dl and the reticulocyte count was 0.4%. The PT and a PTT were 100% and 20.8 sec (control, 24.0 sec). The fibrinogen was 360 mg/dl and the fibrin degredation product was negative (below 8 ug/dl). the haptoglobin level was 217.2 mg/dl. The creatinine clearance was 88.54 ml/min, the urea clearance 40.57 ml/min and the estimate GFR was 65.56 ml/min. Renin was 1.3 ng/ml/hr and aldosteron was 10 pg/ml. The HBsAg was negative and the anti-HBs was positive. IgG 1370, IgA 181, IgM 208, IgE 810 mg/dl, the complement C3 21.8 and the C4 13.4 mg/dl. LE cell was positive. FANA was positive. Anti-ds DNA Ab was above 100IU/ml, the anti-Sm Ab positive, the anti-Ro positive and the anti-La was negative. Antiplatelet antibody was positive. VDRL and RA fator were negative. On the 7th day in hospital, a kidney biopsy was performed and light microscopy showed increased cellularity, segmental necrosis, patent capillary lumen, mild mononuclear cell infiltraion and fibrosis in the interstitium with tubulorrhexis. Immunofluorescent micorscopy demonstrated generalized, diffuse or segmental granular deposition in the mesangium of IgG, IgA, IgM and C3. These are consistent with diffuse proliferative lupus nephritis, WHO class IV (Fig I).

The patient was treated with intravenous cyclophsphamide pulse on the 12th day in hospital and daily oral prednisolone therapy but on the 14th day in hospital, reticulocyte count suddenly elevated (3.0%) and further thrombocytopenia (32,000/mm^3). So, studies were done to search for the cause. The color of serum was red-orange and peripheral blood showed thrombocytopenia and microangiopathic hemolytic anemia (MAHA) with helmet cells and schistocytosis (Fig 2). Total bilirubin was 1.6 mg/dl and direct bilirubin was 0.4 mg/dl. LDH was 860 units. Bone marrow aspi-

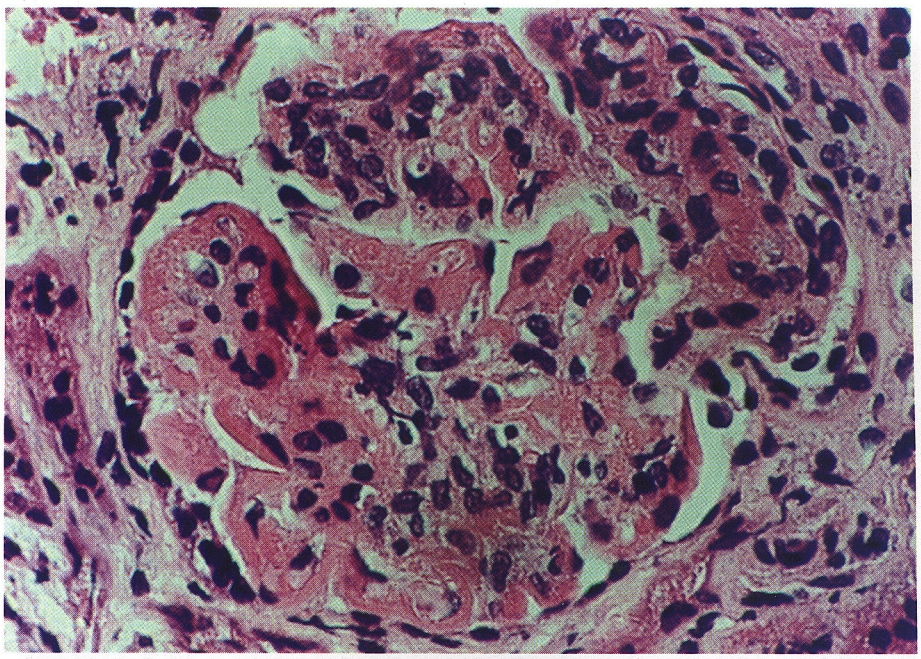

Fig. 1. Kidney biopsy. Light microscopy shows hypercellularity, increased mesangial matrix and basement basement membrane thickening with wire-loop formation, which all consistent with histological changes in diffuse proliferative lupus nephitis (WHO class IV, Hematoxylin & eosin stain, ×400).

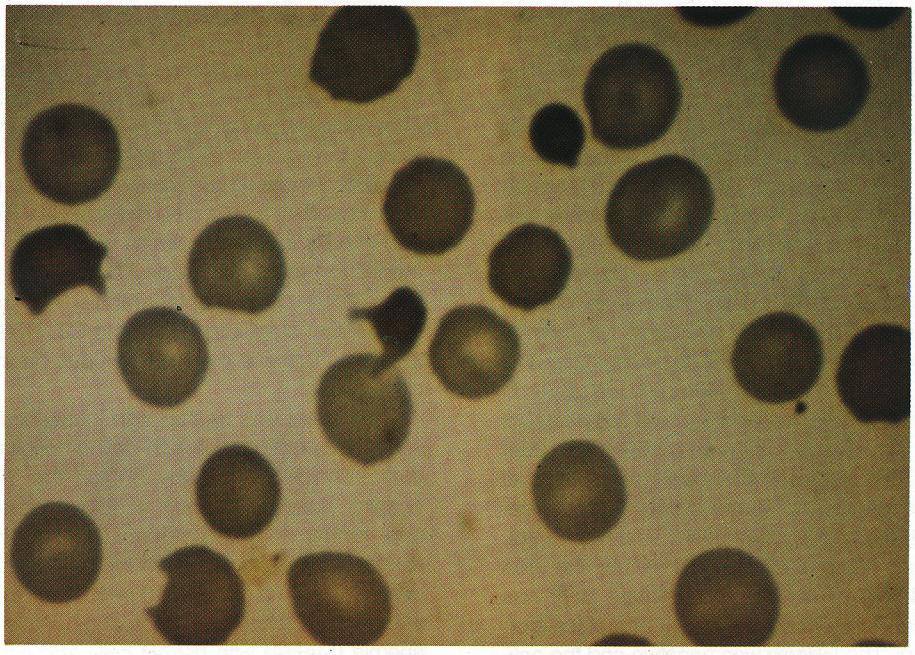

Fig. 2. Blood film showed microangiopathic hemolytic anemia, revealing helmet cell and other fragmented red cell (Hematoxylin & eosin stain, ×1000).

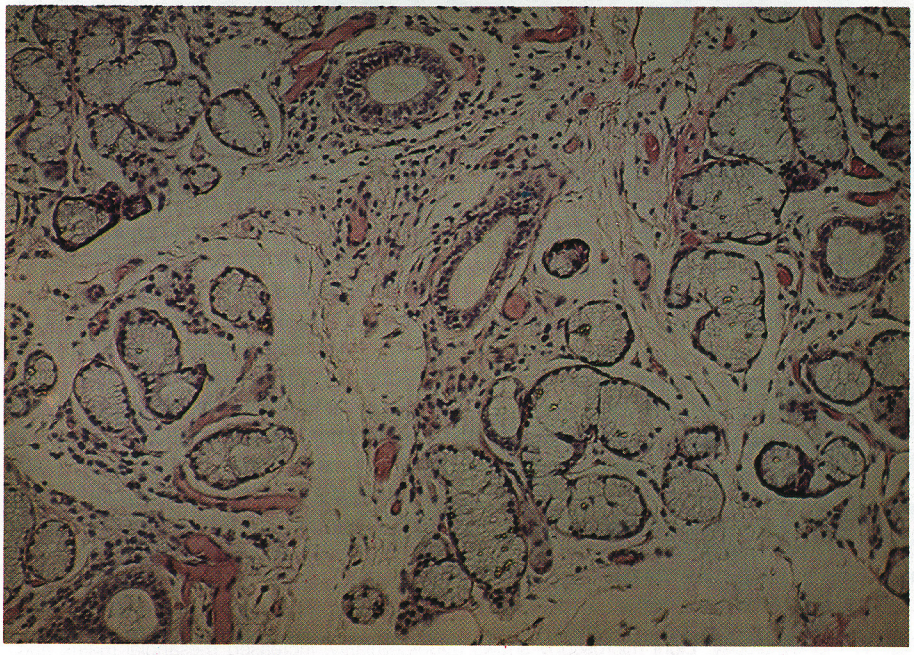

Fig. 3. Gingival biopsy. Numerous small vessels contain fibin thrombi without perivascular inflammatory cell infitration (Hematoxylin & eosin stain, ×100).

ration and biospy showed no definite abmormality. The repeated PT and aPTT were normal. Presuming that this suggested TTP, a biopsy of gum was done and light microscopy demonstrated widespread bland hyaline thrombi occlusion of small vessels (Fig. 3) consistent with the pathologic findings of TTP. Immunofluorescent microscopy of the skin revealed fine granular or liner deposition of IgG, IgA, IgM, C3 at the dermo-epidermal junction (lupus band).

While we continued the monthly intravenous cyclophosphamide pulse therapy with oral prednisolone administration for SLE, we started daily plasmapheresis with fresh frozen plasma infusion (total 21 times, from HD 30 to HD 60) for TTP until the clinical features of MAHA, such as fragmented erythrocyte, elevated LDH level and elevated reticulocyte count, had subsided (Fig 4).

The clinical and serologic activity of SLE and TTP decreased and general symptoms subsided. MAHA in peripheral blood converted to a negative finding (HD 72). The patient has returned to full normal acitvity at 4 months after the start of treatment.

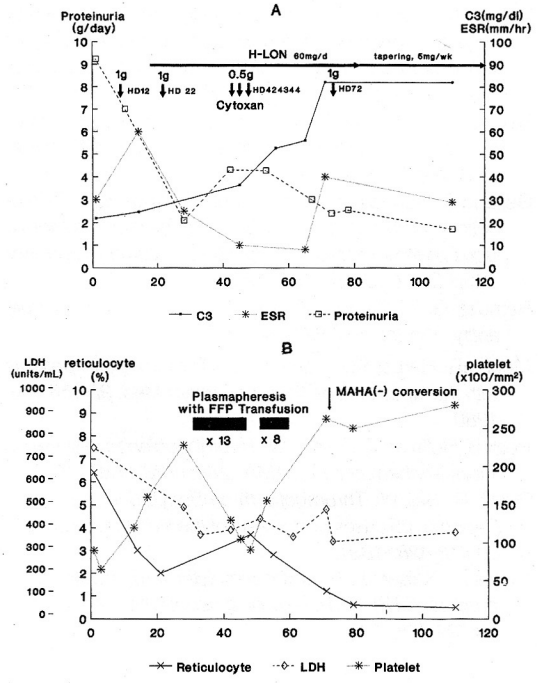

Fig. 4. Scheme of treatment modalities and sequential changes of clinical findings. (A) Sequential changes of C3, proteinuria and ESR which reflect the activity of SLE. (B) Sequential changes of LDH, reticulocyte and platelet which reflect the activity of TTP.

DISCUSSION

TTP was first described by Moschcowitz in 1925. It is characterized by the features of hemolytic anemia with microaniopathic changes in erythrocytes, thrombocytopenia, flucturation neurological abnormalities, fever, and renal disease. The typical pathological lesion is widespread bland hyaline occlusions of small arterioles. The etiology or pathogenesis is entirely unknown. By histochemical and electron microscopic techniques the thrombi have been found to consist primarily of fibrinogen and fibrin (Feldman et al., 1966). Umlas and Kaiser (1970) have made a suggestion that TTP is not a disease entity but a syndrome that can occur in the course of diseases affecting the microcirculation.

Hemolytic-uremic syndrome (HUS) quite closely resembles TTP. Histologically, fibrin-like material is usually present in the renal vessels. Although attempts have been made to differentiate HUS from TTP, none of the proposed differentiating features can clearly separate these two clinical syndromes. Recently some authors hae favored a term for HUS/TTP which describes different clinical expressions of a single disease entity (Remuzzi, 1987).

Unfortunately, there is a considerable overlap between SLE and TTP both on clinical, and pathologic grounds. The two diseases do differ significantly, however, in sex incidence, clinical course, duration, complications and prognosis. Also the LE phenomenon is reported to be positive only seven times (11 per cent) in 64 reported patients with TTP (Amorosi Ultmann, 1966).

Similarly, the occurrence of hyaline thrombi in established autopsy cases of SLE wihout the clinical symptoms of TTP is rare (Dekker et al., 1974).

When prior reports of the assocication of SLE and TTP are analysed by the 1982 ARA criteria for SLE only four patients can be identified who had unequivocal SLE clinically and subsequently developed TTP. A fifth patient developeed both SLE and TTP concurrently (Dekker et al., 1974).

Although TTP occasionally complicates the course of SLE, the pathogenesis of TTP in these patients is not well understood. Patients with SLE may develop disturbances in blood coagulation and lupus patients with circulating anticoagulants may be at risk from thrombotic events (Meuh et al., 1980).

The diagnosis of TTP may be difficult in patients with SLE because of the overlapping manifestations of the two disorders. Anemia, thrombocytopania, fever, neu-

rological abnormalilty, and renal disease all occur in SLE as well as in TTP.

The thrombotic events in SLE are very likely multifactorial in etiology. But, we favor the view that immunologic injury of endothelial cells and production of antiendothelial antibody or platelet aggregating factors in SLE may induce the thrombotic sequences. An additional abnormality found in SLE but not in TTP is the presence of anticardiolipin (lupus anticoagulant), an antibody that impairs conversion of prothrombin to thrombin through reaction with phospholipids, which has been associated with thrombotic tendencies (Carerras et al., 1981).

The pathophysiological defects in TTP are unknown but experimental data provide some explanation for the clinical use of plasma infusion for treatment. In the past, many patients with TTP have been refractory to treatment regimens including corticosteroids, cytotoxic agents and splenectomy. The plasma of patients with TTP appears to be unable to stimulate prostacyclin formation under experimental conditions. This defect is corrected by in vivo plasma infusion. Plasma also appears to inhibit the activity of a platelet aggregating factor (Gelfand et al., 1985).

Among the 1982 American Rheumatism Association (ARA) criteria for the classification of SLE, in this case, there were malar rash, oral ulcer, arthritis, renal disorders (proteinuria), neurologic disorder (headache), hematologci disorders (anemia, leukopenia, lymphopenia, thrombocytopenia), immunologic disorders (anti-dsDNA Ab, anti-Ro Ab, antiplatelet Ab, LE cell, anti-Sm Ab, LE cell). futhermore, biopsies of the skin and kidney demonstrated lupus band and lupus nephritis. Alterantively, it is suggested that hemolytic anemia with microangiopathic changes in erythrocytes, elevated reticulocyte count, increased LDH level, thrombocytopenic purpura, renal disease (mild azotemia), fever and suspicious neurological abnormality (headache) at clinical bases and widespread bland hyaline thrombi occlusion of small arterioles of gum at histological bases indicated TTP.

Also, SLE could induce hemolytic anemia and thrombotic tendencies. But the mechanism of hemolytic anemia in SLE is autoimmune nature and Coombs' tests are alwasys positive. Alternatively, thrombotic microangiopathy due to necrotizing vasulitis in SLE could be excluded in this case because vessels in gum and renal biopsy do not show vasular necrosis and leukocyte infiltration which are pathognomic features of necrotizing vasulitis. It is possible that thrombotic manifestations due to anticardiolipin (lupus anticoagulant) are excluded because VDRL was negative in the patient (anticardiolipin reacts with the phospholipid component of reagents used for VDRL, so that the negativity of VDRL indirectly indicates the absence of anticardiolipin). Thus, the above findings were thought to show the coexistence of TTP and SLE in this patient.

After combined treatment of corticosteroid, cyclophosphamide and plasmapheresis with fresh frozen plasma infusion, the activity of SLE and TTP in the patient decreased and general symptoms improved.

REFERENCES

Amorosi E, Ultmann J: *Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine 45:139-159, 1966*

Carreras L, Machin S, Deman R: *Arterial thrombosis, intrauterine death and lupus andticagulant detection of immunoglobulin interfering with prostacyclin formation. Lancet 1:244-246, 1981*

Dekker A, O'Brien ME, Cammarata RJ: *The association of thrombotic thrombocytopnic purpura with systemic lupus erythematosus; A report of two cases with successful treatment of one. Am J Med Sci. 267:243-249, 1974*

Feldman JD, Mardiney MR, Unanue ER: *The vascular pathology of thrombotic thrombocytopenic purpura. Lab Invest. 15:927-946, 1966*

Gelfand J, Truong L, Stern L, Pirani CL, Appel GB: *Thrombotic thrombocytopenic purpura syndrome in systemic lupus erythromatosus: Treatment with plasma infuion. Am J Kid Dis. 6 (3):154-160, 1985*

Remuzzi G: *HUS and TTP: Variable expression of a single entity. Kid Int. 32:292-308, 1987*

Meuh JR, Herbst KD, Rapaport SI: *Thrombosis in patients with the lupus anticoaglant. Ahn Intern Med. 92:156-159, 1980.*

Peck B, Hoffman G, Franck W: *Thrombophlebitis in systemic lupus erythematosus. JAMA. 240:1728-1730, 1978.*

Ridolfi R, Bell W: *Thrombotic thrombocytopenic purpura: Report of 25 cases and review of the literature. Medicine 60:413-428, 1981.*

Umlas J, Kaiser J: *Thrombohemolytic thrombocytopenic purpura (TTP): a disease or a syndrome? Am J Med. 49:723-728, 1970.*