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Case Report

Thrombotic Thrombocytopenic Purpura and Systemic Lupus Erythematosus: a Rare and Life-threatening Association

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Abstract

Introduction: The association between thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) is uncommon. Diagnosis is often difficult because of their clinical and biological similarities. The presence of TTP in SLE worsens the prognosis and causes high mortality in the absence of early therapeutic interventions.

Case report: We report the case of a 20 year-old man, admitted with nephrotic range proteinuria, hematuria and rapidly progressive renal failure. He also had anemia, thrombocytopenia and pericardial effusion. The diagnosis of SLE was made based on these clinical findings along with positive antinuclear and anti dsDNA antibodies. Renal biopsy revealed class IV/ V lupus nephritis (LN) with active lesions of thrombotic microangiopathy. The evolution of neurological deficit, persistent thrombocytopenia and active microangiopathic changes suggested the diagnosis of associated TTP. The patient was treated initially with corticosteroids and cyclophosphamide. Plasmapheresis could only be started 16 days later. Mycophenolate mofetil and rituximab were successively tried in the absence of improvement in renal function and persistent thrombocytopenia. The patient's neurological condition deteriorated necessitating transfer to the intensive care unit and mechanical ventilation. There he developed pneumonia and died of septic shock two months after presentation.

Conclusion: The coexistence of TTP and SLE needs to be considered early in SLE patients with complicated course. It may not respond to the conventional immunosuppressive treatment of SLE.

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Introduction

The association of thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) is extremely rare with an incidence estimated at 0.5 % [1]. The presence of TTP in SLE worsens the prognosis and increases mortality, necessitating early therapeutic intervention.

In TTP, a constitutional or acquired deficiency of the activity of protease (ADAMTS-13) of von Willebrand factor is noted. ADAMTS-13 is a zinc metalloprotease which cleaves a high molecular weight complex called "ultra-wide complex of von Willebrand factor" in the circulating blood. ADAMTS-13 has a well demonstrated antithrombotic effect and its deficiency leads to accumulation of multimeric forms of high molecular weight von Willebrand factor. This promotes platelet adhesion and aggregation leading to the formation of vascular microthrombosis. ADAMTS-13 deficiency has been demonstrated in more than 80% of patients with acquired forms of TTP [2]. The remaining cases correspond to a deficit-free TTP for which the pathophysiology remains unclear. The high prevalence of anti-ADAMTS-13 antibodies in autoimmune diseases such as SLE is known to lead to reduced ADAMTS-13 activity [3]. Moreover, the activation of the classical complement pathway has been implicated in the induction of thrombotic microangiopathy in lupus nephritis as evidenced by glomerular C4d deposits [4]. The diagnosis of TTP in SLE patients is difficult because of their clinical and biological similarities; hemolytic anemia, thrombocytopenia, neurological deficit, fever and renal dysfunction. The presence of schistocytes or fragmented granulocytes (GR) is an element in favor of TTP [5, 6].

Figure 1: Glomerulus with endocapillary proliferation (EP) and intracapillary thrombi (T). Light microscopy (x 400 trichrome stain)

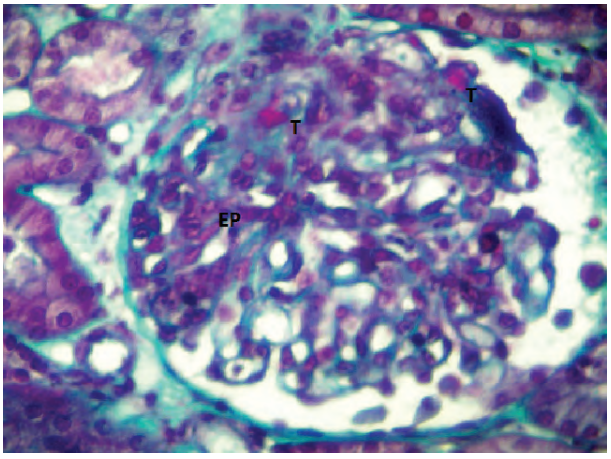
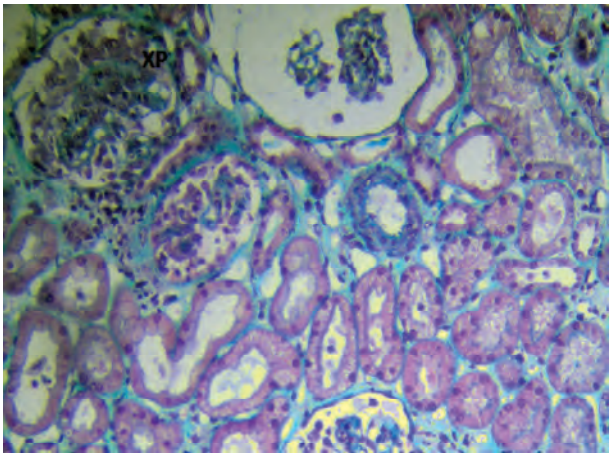


Figure 2: Glomerulus with extracapillary proliferation (XP). Light microscopy (x 250 trichromestain)



Case presentation

Here we report the case of a 20 year-old man with no significant past medical or surgical history who presented complaining of generalized body swelling of one month duration. He also complained of non-pruritic rash affecting the trunk and upper limbs. On physical examination, he was conscious, fully alert and oriented. He had facial swelling and bilateral lower limb edema. He was not febrile and his blood pressure was 130/80 mmHg. Neurological examination was not remarkable apart from brisk tendon reflexes. He had a maculo-papular rash affecting the trunk and upper limbs. The rest of the physical examination was unremarkable.

The laboratory workup revealed active urinary sediment with protein 2+ and blood 3+. His urinary protein excretion was 5.5 g/day, serum protein 5.7 g/dl, serum albumin 2.3 g/dl, serum creatinine 3.5 mg/dl and creatinine clearance 40 ml/minute. A complete blood count revealed normochromic normocytic anemia with hemoglobin of 8.2 g/dl and reticulocyte count of 44200/µl, thrombocytopenia with platelet count of 75 000/µl and leukopenia with WBC of 2800/µl. Schistocytes were positive at 3% and direct Coomb's test was negative. Bone marrow examination was normal. The LDH was two and a half times the normal value. Viral serologies were negative and complement levels were normal. He had a positive antinuclear antibody (ANA) with a titer of 1:640 IU/ml. Anti double stranded DNA (dsDNA) antibody level was elevated at 251U/ml and antiphospholipids antibody (APL) level was 21 IU/ml. Chest X-ray was normal. Renal ultrasound showed increased size of both kidneys. The renal Doppler study was normal. Echocardiography showed pericardial effusion with a thickness of 14 mm.

The diagnosis of SLE was made based on renal, hematological and cardiac involvement together with positive ANA and anti- ds-DNA antibodies. The SLE disease activity index (SLEDAI) score on admission mounted to 15. The patient received three pulsed doses of methylprednisolone followed by oral prednisolone, after which pancytopenia was corrected. Renal biopsy was taken and it revealed class IV / V lupus nephritis with active lesions of thrombotic microangiopathy (TMA) (Figures 1-2). Cyclophosphamide was started at a dose of 0.75g/m^2 along with supportive hemodialysis. The patient received fresh frozen plasma infusions but plasmapheresis was only available after 16 days of admission. At day-20, evolution was marked by severe neurological deterioration with right temporal hypo-dense lesions on CT brain and recurrence of thrombocytopenia. At this stage, the presence of microangiopathic hemolytic anemia, impaired neurological status and persistent thrombocytopenia suggested the diagnosis of TTP associated with SLE. After one month of treatment the patient remained anuric and continued to have severe thrombocytopenia with platelet counts < 50000/mm^3. Cyclophosphamide was substituted with mycophenolate mofetil (MMF). At day 45, salvage therapy with rituximab (500 mg first dose) was tried in the absence of improvement in renal function and persistent thrombocytopenia. Three days later, the patient developed convulsions, supraventricular tachycardia and respiratory distress that required his transfer to the intensive care unit (ICU) and mechanical ventilation. During his stay in the ICU, he developed pneumonia and died of septic shock 19 days after ICU admission.

Discussion

In this case, the presence of microangiopathic hemolytic anemia, impaired neurological status and persistent thrombocytopenia suggested the diagnosis of TTP associated with SLE. The association TTP and SLE is extremely rare and serious [1, 7]. The activation of the classical complement pathway has been implicated recently in induction of thrombotic microangiopathy in lupus nephritis as evidenced by glomerular deposits of C4d [4]. In this case complement level was normal but C4d stain was not available.

The prognosis of TTP has significantly improved by plasma exchange (PE) compared to treatment with fresh frozen plasma (FFP) alone, with the survival rate increasing from 10% to 75-92% [1]. The therapeutic benefit of PE is achieved through a transfusion effect and a subtractive effect. Transfused plasma provides the deficient factor ADAMTS-13 while plasmapheresis removes the mega multimers of von Willebrand factor and any circulating autoantibodies. The British Committee for Standards in Hematology recommends that PE therapy continues for a minimum of two days after the return of platelet counts to normal, normalization of neurological status, increased hemoglobin and normalization of LDH [1]. The residual presence of schistocytes in the peripheral blood after normalization of platelet count is common and is not predictive of relapse [8]. Rituximab (RTX) is a humanized monoclonal antibody directed against B lymphocytes. Some reports suggest that RTX is a promising therapy in severe lupus nephritis refractory to other immunosuppressive therapies [9]. RTX is also recommended in the treatment of relapsing or refractory forms of TTP [10].

In our case, although plasma exchange was considered early in the course of the disease, it became available only 16 days later. This delay could have contributed to the neurological deterioration and worsening thrombocytopenia. Immunosuppressive therapy consisting initially of cyclophosphamide and corticosteroids, and later MMF and RTX, was used for the treatment of proliferative lupus nephritis. It was well tolerated, but didn't improve the patient's condition. TTP with multi-organ failure is associated with a high mortality of about 35%. In this context, neurological impairment is a poor prognostic feature [11].

Conclusion

TTP diagnosis is difficult in the context of SLE because of similarity between the two pathologies. This diagnosis must be considered early because early diagnosis and prompt treatment may have a positive impact on prognosis.

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