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CASE REPORT

**Yasuaki Hayashino · Hiroyasu Ishimaru · Kazuhiro Hatta**
**Yosiaki Kohri**

# Thrombotic thrombocytopenic purpura as an etiology of thrombocytopenia in systemic lupus erythematosus: case report

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**Abstract** Thrombotic thrombocytopenic purpura (TTP) is an unusual complication of systemic lupus erythematosus (SLE). Although the reported association between SLE and TTP is increasing, a few cases do improve without plasmatherapy. We report a case of TTP which was successfully treated without plasmatherapy, which might be underestimated as an etiology of thrombocytopenia in SLE. TTP should always be considered as a concomitant disease when Coombs' negative hemolytic anemia or thrombocytopenia is seen in SLE patients.

**Key words** Systemic lupus erythematosus (SLE) · Thrombocytopenia · Thrombotic thrombocytopenic purpura (TTP)

## Introduction

Thrombotic thrombocytopenic purpura (TTP) was first described by Moshcowitz in 1924,[1] and was thought to be only rarely associated with systemic lupus erythematosus (SLE).[2,3] Since both processes may present with some or all elements of the five classic symptoms considered pathognomonic of TTP, a diagnosis of TTP as a syndrome distinct from SLE is not definitive. These five symptoms are microangiopathic hemolytic anemia, thrombocytopenia, fever, neurological deficit, and renal abnormality. Further distinct syndromes exist with renal thrombotic microangiopathy, such as disseminated intravascular coagulation (DIC), malignant hypertension, and antiphospholipid syndrome (APS).[4,5] It is now postulated that TTP is due to an inhibitor of von Willebrand's factor-cleaving protease, or a constitutional deficiency of the protease, and plasma therapy has a significant impact on survival in TTP.[6,7] However, it remains uncertain whether the pathogenesis or appropriate therapy is the same for SLE. We report here the case of a female patient with a mild case of TTP in SLE who was successfully treated without plasmatherapy, and we briefly discuss the relation between TTP and SLE.

Y. Hayashino[1] (✉) · H. Ishimaru · K. Hatta · Y. Kohri
Department of Comprehensive Medical Care and Management, Tenri Yorozu Hospital, 200 Mishima, Tenri 632-8552, Japan

*Present address:*
[1] Department of General Medicine and Clinical Epidemiology, Kyoto University Graduate School of Medicine, 54 Kawahara, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
Tel. +81-75-751-4248; Fax +81-75-751-4211
e-mail: ya-su@mvd.biglobe.ne.jp

## Case report

A 27-year-old Japanese woman was admitted to our hospital with worsening edema of the lower legs. Four months before admission, she had been suffering from hypertension and edema of the lower legs following her first delivery. Her symptoms initially improved, but two months before admission she again began to suffer from gradually worsening edema of the lower legs. She had not been aware of any fever. She had a severe headache, but never complained of any seizure. A physical examination showed that she was obese, but otherwise of good appearance; her temperature was 37.9°C, her blood pressure was 150/90 mmHg, and her heart rate was 80 beats/min. She was alert, well oriented, and showed no acute distress. Her conjunctivae were pale, but not icteric. Examination of the head and neck revealed no erythema, no lymphadenopathy, no oral ulceration, and no purpura of the oral mucosa. Her lower legs showed severe pitting edema. Neurological examination found no abnormality.

Laboratory studies showed hemoglobin at 5.6 g/dl, a white cell count of 4300/cm$^3$ with left shift, a platelet count of 19000/mm$^3$, and a reticulocyte count of 5.9%. The direct and indirect Coombs' tests were negative. Her haptoglobin level was 1.3 mg/dl, and her serum hemoglobin was 53.9 mg/dl. A peripheral smear showed many schistocytes (15%) (Fig. 1). Her fibrinogen level was 230 mg/dl (normal 170–330), FDP was 36 μg/dl (normal <5), and FDP D-dimer was 17 μg/ml (normal <1). The prothrombin time and partial thromboplastin time were both normal. Biochemical tests

showed creatinine at 1.3 mg/dl, lactic dehydrogenase (LDH) of 1234 IU/l, and bilirubin at 0.7 mg/dl (indirect 29%). Her anti-dsDNA antibody level was 93 IU/ml (normal <10), and anti-DNA antibody (RIA) was above 300 IU/ml; the antinuclear antibody measure was positive at 1:1280 for both homogeneous and specked patterns. Lupus anticoagulant (dilute Russell Viper venom time method), β-2-glycoprotein I, and VDRL were all undetectable. Surface platelet associated IgG (PAIgG) was 43% (microenzyme-linked immunosorbent assay, normal <30%). Other autoantibodies were negative, including anti-RNP antibody, antiSm antibody, antiSS-A antibody, and antiSS-B antibody. Serum CH50, C3, and C4 complements were all greatly reduced, at 9.0 CH50 (normal 29–45), 10.5 mg/dl (normal 60–150), and 2.9 mg/dl (normal 3–39), respectively. Tests for von Willebrand's factor (vWF) and von Willebrand's factor-cleaving protease (vWFCP) were not performed. Urinalysis showed 4+ albuminuria with dysmorphic red cells. A 24-h urine collection contained 6840 mg protein. We also performed computed tomography of the brain in view of the patient's headache, but it proved to be normal.

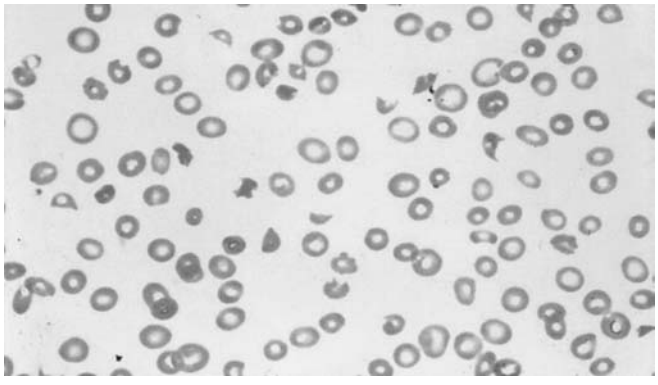

**Fig. 1.** Schistocytes in a peripheral blood smear on admission

We considered that the pathogenesis of thrombocytopenia was thrombotic microangiopathy in view of the hemolytic anemia and schistocytes. A diagnosis of SLE was made on the basis of positive anti-DNA antibody, positive antinuclear antibody, hematological abnormality, and renal impairment. We also made a diagnosis of TTP based on thrombocytopenia and microangiopathic hemolytic anemia, as suggested by her elevated LDH and the many schistocytes in a peripheral blood smear. Treatment began with prednisolone at 60 mg/day, and with dipyridamole and angiotensin-converting enzyme inhibitor on day 2. The thrombocytopenia then began to improve. Following this improvement, the anemia and schistocytes also gradually improved. Despite these hematological improvements, however, proteinuria did not decrease. We therefore pulsed using methylprednisolone (1 g/day for 3 days) and cyclophosphamide (500 mg/m$^2$ body surface area) monthly for lupus nephritis. A renal biopsy was performed on day 12, when the platelet count had recovered to 155000 mm$^3$. Electron microscopy showed diffuse proliferative glomerulonephritis which was consistent with World Health Organization class IV lupus nephritis. There was no evidence, such as intravascular thrombi, for renal damage due to TTP. The levels of blood urea nitrogen (BUN) and creatinine, which worsened after the first pulse therapy, improved after the second methylprednisolone and cyclophosphamide pulse therapy, and the patient was discharged on day 76. After discharge, we performed methylprednisolone and cyclophosphamide therapy monthly for 6 months, including in-patient therapy. The test results at an outpatient clinic on day 188 were Hb 11.7 g/dl, platelets 2230000/mm$^3$, LDH 236 IU/l, creatinine 0.9 mg/dl, and no schistocytes observed in the peripheral blood smear. A 24-h urine collection contained only 650 mg protein. Figure 2 summarizes the patient's clinical course. The patient is now

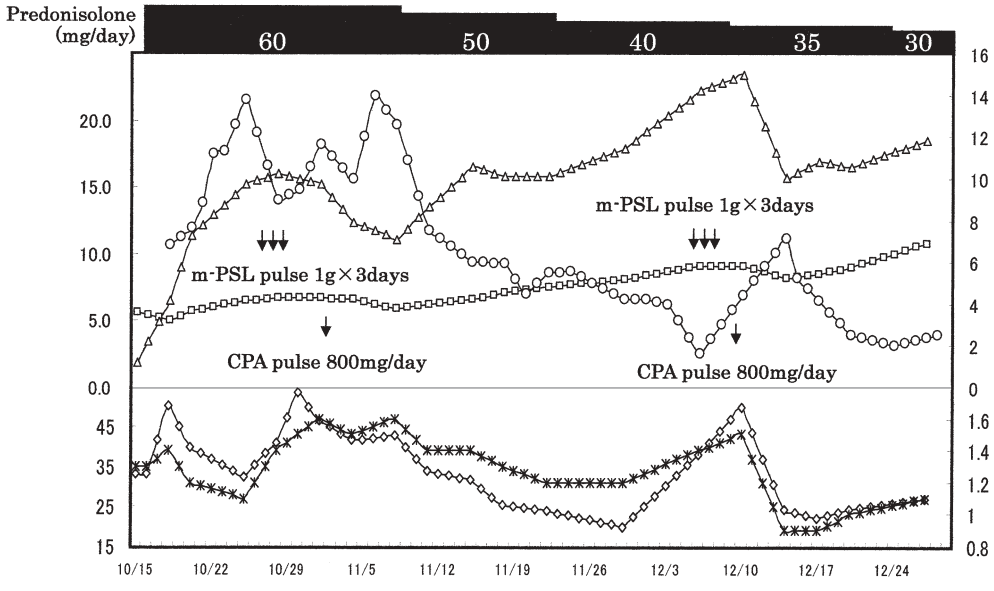


**Fig. 2.** Summary of the relation between therapeutic procedures and laboratory studies. *m-PSL*, methylprednisolone; *CPA*, cyclophosphamide. *Squares*, hemoglobin (*Hb*) (g/dl); *triangles*, platelets (×10$^4$/μl); *diamonds*, blood urea nitrogen (*BUN*) (mg/dl); *circles*, protein in 24-h urine collection (g/day); *stars*, creatinine (*Cr*) (mg/dl)

receiving low steroid doses (prednisolone 15 mg/day), and the SLE is clinically and serologically inactive.

## Discussion

This patient presented with manifestations of SLE and TTP. She fulfilled the 1982 American Rheumatism Association (ARA) criteria for the classification of SLE, and also the characteristic clinical picture of TTP, with microangiopathic hemolytic anemia in the presence of normal coagulation parameters, and profound thrombocytopenia.[8] The review by Amorosi and Ultman in 1996[9] set out the five classic clinical features of TTP: (1) microangiopathic hemolytic anemia; (2) thrombocytopenia; (3) neurological symptoms and signs; (4) renal function abnormalities; (5) fever. In the last 20 years, the availability of plasmapheresis has created an urgency for a diagnosis, which in turn has required less stringent diagnostic criteria. This need has reduced the stringency of diagnostic criteria from the five classic clinical features to the current two.[10] In fact, recent studies have required only the presence of microangiopathic hemolytic anemia and thrombocytopenia to support the diagnosis, without clinically apparent signs.[11,12] Although this case did not satisfy the classic criteria, we made a diagnosis of TTP in accordance with the recent trend.

Reports suggesting a relation between TTP and SLE, which were thought to occur together only rarely, have recently been accumulating.[13] When schistocytes and elevated lactate dehydrogenase are also present in SLE patients, thrombotic microangiopathy should be considered. Neisher et al.[13] reported that TTP preceded the diagnosis of SLE in two cases, and diagnoses were made simultaneously in two cases. Although TTP presented simultaneously with SLE in our patient, in most cases TTP presents long after the diagnosis of SLE is established.

In spite of its apparent rarity, the diagnosis of TTP in SLE could be important in selecting a therapy. There are no well-established guidelines for the treatment of this condition. Steroid therapy appears to be inadequate to control the process in most patients.[13] Furthermore, patients might either deteriorate or progress under steroid treatment, even at high doses.[14–16] Based on reviews of the published cases of TTP in SLE, plasmapheresis or plasma infusion appear to be beneficial adjuncts to therapy with steroids, as in classical TTP.[13,17]

Recent observations suggest that a deficiency of von Willebrand's factor-cleaving protease, or of inhibitory antibodies against von Willebrand's factor-cleaving protease, are strongly associated with the pathogenesis of classical TTP.[6,7] This is why plasma therapy is effective for the treatment of TTP. In our case, on the other hand, plasmatherapy was not necessary because the patient's thrombocytopenia began to improve after the initial dose of oral prednisolone. Our case allows us to make a further inference about the pathogenesis of TTP in SLE. Autoantibodies against von Willebrand's factor may contribute to the pathogenesis of TTP in SLE, and prednisolone and cyclophosphamide may

**Table 1.** Review of reported cases of TTP simultaneously diagnosed with SLE in adults

| Reference | Age/sex | ANA | Anti-DNA | Other | TTP features | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Nesher et al.[13] | 22F | (+) | (+) | RBx: TTP | A, T, R, F | Steroids, PE, CPA | Recovery |
| | 39F | (+) | (+) | Coombs'(−), APL(−) | A, T, R, N, F | Steroids, PE, CPA | Recovery |
| Musio et al.[21] | 46F | (+) | (+) | RBx: lupus nephritis (IV) and TTP, APL(+) | A, T, R, N, F | Steroids, PE | Death |
| Caramaschi et al.[22] | 35F | (+) | (−) | aCL(−) | A, T, R, N, F | Steroids, PE | Recovery |
| Gelfand et al.[23] | 21F | (+) | (−) | RenalBx: lupus nephritis (III) and TTP | A, T, R, N, F | Steroids, PE, AZ | Recovery |
| Perez-Sanchez et al.[24] | 17M | (+) | (+) | RBx: lupus nephritis (IV) | A, T, N, F | Steroids, PE, CPA, AZ | Recovery |
| Vaidya et al.[25] | 34F | (+) | (−) | APL(−), RBx: TTP | A, T, R | Steroids, PE, CPA, VCR | Death |
| Present case | 27F | (+) | (+) | Coombs'(−), aCL(−), RBx: lupus nephritis (IV) | A, T, F | Steroids, CPA | Recovery |

RBx, renal biopsy; A, microscopic hemolytic anemia; T, thrombocytopenia; N, neurological sign; R, renal disease; F, fever; PE, plasmapheresis or plasma infusion; CPA, cyclophosphamide; VCR, vincristine; AZ, azathioprine; APL, antiphospholipid antibody; aCL, anticardiolipin antibody; III/IV, World Health Organization class III/IV

improve TTP in SLE, without plasmatherapy, by suppressing the production of these antibodies, although these relations have not been discussed in previous reports.

The diagnosis of TTP complicated by SLE is complex and difficult for several reasons. First, several similarities exist between the clinical features of SLE and TTP, including hemolytic anemia, thrombocytopenia, fever, renal disease, and neurological symptoms. Second, thrombotic microangiopathy accompanying SLE also indicates a concomitant disease process such as antiphospholipid syndrome, scleroderma, malignant hypertension, or cyclosporine nephrotoxicity.[4,5] Third, it is reported that PaIgG can be detected at a high level even in the case of TTP without concomitant SLE. Although the pathogenesis of thrombocytopenia is commonly attributed to autoimmunity in the presence of PaIgG, it cannot be determined so simply in the case of TTP in SLE. Therefore, in the presence of hemolytic anemia and many schistocytes, we considered that the real cause of thrombocytopenia was TTP.

Two earlier reported cases of TTP complicated with SLE have been treated successfully without plasmatherapy.[18,19] We ask: Are those cases which improved without plasmatherapy very rare? Although the incidence of TTP occurring in the setting of SLE has been reported to be as low as 0.5%,[20] cases of mild TTP might be underdiagnosed in SLE. We summarize reported cases of TTP diagnosed concomitantly with SLE in Table 1.[13,21–25] In these, our case is considered to be a relatively mild case of TTP, since the patient had only three symptoms of the classic five symptoms, and improved without plasmatherapy. In addition to that, Devinsky et al.[26] found pathological changes consistent with TTP in 14% of patients in a review of the medical and autopsy records of 50 consecutive SLE patients, all of whom had retrospective clinical evidence of TTP. Based on those observations, we suggest that cases of mild TTP, like the one reported here, occur more frequently as an etiology of thrombocytopenia in SLE.

We believe that there are two keys to the confirmation of TTP in SLE. First, it is relatively difficult to detect schistocytes in a peripheral blood smear, so there is a tendency to miss or underdiagnose unless great care is taken. Hemolytic anemia is generally Coombs'-positive in SLE, but negative in TTP.[27] When Coombs' negative anemia is seen in SLE, we should look systematically for schistocytes. Second, thrombocytopenia is much easier to find than schistocytes, and is a useful key to find thrombotic microangiopathy in SLE. We should therefore always think about TTP as a differential diagnosis when thrombocytopenia is found in SLE patients, in addition to autoimmune thrombocytopenia and antiphospholipid syndrome.

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