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Thrombotic thrombocytopenic purpura as a rare complication in childhood systemic lupus erythematosus: case report and literature review

血栓形成的血小板減少紫癜作為一種兒童期系統性紅斑狼瘡罕見的併發症：病例報告和文獻回顧

Thrombotic thrombocytopenic purpura is a rare but serious condition in childhood. It can be idiopathic or a complication of other diseases or drug therapy. We report on a 12-year-old Chinese girl who presented with fulminant systemic lupus erythematosus with progressive renal failure, pancytopenia, and cerebral dysfunction due to thrombotic thrombocytopenic purpura. The patient also had *Pneumocystis carinii* pneumonia, *Pseudomonas* septicaemia, and *Herpes zoster* infections as a result of immunosuppressive treatment. She responded to combined therapy with pulse methylprednisolone, cyclophosphamide, plasmapheresis, and intensive care support, and completely recovered renal and neurological function. A review of the English-language medical literature since 1968 identified 20 other paediatric cases of systemic lupus erythematosus and thrombotic thrombocytopenic purpura. Clinical features, treatment, and outcome of these cases are presented and discussed. Early recognition is important, and although plasmapheresis is not of proven benefit in severe cases of systemic lupus erythematosus, it is life-saving in lupus-related thrombotic thrombocytopenic purpura and must be instituted early to avoid a poor outcome.

兒童患上血栓形成的血小板減少紫癜是一種罕見但嚴重的疾病，它可以是自發的，也可以由其他疾病或藥物治療引致。本文報告的病例是一個12歲的華裔女童，她患上暴發性的系統性紅斑狼瘡及血小板減少紫癜，以及後者引起的腎衰竭、全血細胞減少以及大腦機能障礙。而使用抑制免疫力的治療方法又引致病童患上間質性漿細胞性肺炎、假單細胞屬敗血症，以及帶狀疱疹。我們以靜脈滴注甲基潑尼松龍、環磷酰胺及血漿提取作綜合治療，並給予加護服務。病童對治療反應良好，腎功能和神經功能完全回復正常。本文同時回顧了自1968年起至今的英語醫學文獻，發現20個系統性紅斑狼瘡及血栓形成的血小板減少紫癜的兒科病例，並介紹和探討了這些病例的臨床病徵、治療方法及結果。盡早確定病症非常重要。儘管血漿提取對嚴重系統性紅斑狼瘡的治療效用未被證實，但對於血栓形成的血小板減少紫癜患者卻起著救生作用。此方法必須及早施用，否則效果不大。

Key words:
Lupus erythematosus, systemic;
Plasmapheresis;
Purpura, thrombotic thrombocytopenic

關鍵詞：
紅斑狼瘡，系統性；
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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterised by skin lesions, polyarthritis, polyserositis, nephritis, and pancytopenia, all mainly due to immune damage by autoantibodies or immune complex deposition. The disease commonly affects adolescent girls and young adult females, especially among Chinese and Hispanic populations. With the recent development of effective immunosuppressive regimens, the prognosis has dramatically improved. In one study, the risk of mortality due to SLE was 10.1 times as compared with mortality in the general population in 1970 to 1977; in 1986 to 1994, this figure decreased to 3.3.[1]

Thrombotic thrombocytopenic purpura (TTP) is a rare microvascular occlusive disorder and was first described in 1924.[2] It is characterised by the classic pentad of thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, renal abnormalities, and fever. Its estimated incidence was 3.7 per million population in the United States; fewer than 10% of cases occurred in children.[3] The mortality (without treatment) was initially 90%, but with effective treatment by plasmapheresis, it has recently decreased to about 10%.[4]

Thrombotic thrombocytopenic purpura can be primary or secondary to drug therapy (such as mitomycin, cyclosporine, tacrolimus, and quinine), marrow or organ transplantation, or autoimmune diseases. Of the autoimmune diseases, SLE is the most well recognised, and SLE and TTP may precede each other by a variable period of time.[5]

We describe a Chinese girl with fulminant SLE complicated by TTP. Prompt recognition of these coexisting severe conditions led to appropriate treatment with plasmapheresis and aggressive immunosuppressive therapy. Despite the high mortality associated with having both conditions, the patient made a complete recovery with complete return of renal function.

Case report

A 12-year-old girl presented with 4 weeks' history of malar rash, oral ulcers, proteinuria of 10 g/d, haematuria, generalised oedema and hypertension, pericardial effusion, and pleural effusion. Her serum creatinine level was 167 μmol/L on admission, increasing to 231 μmol/L in the following week (reference range, 53-106 μmol/L). She also had pancytopenia with a haemoglobin level of 56 g/L, white blood cell count of 4.5 x 10^9 /L, and a platelet count of 76 x 10^9 /L. Serological test results were positive for antinuclear antibodies (ANA) with a titre of 2560 and a homogeneous fluorescent pattern, and also detected antibodies against double-stranded DNA. The serum complement C3 level was low (0.23 g/L; reference level, >0.8 g/L), as was the C4 level (0.10 g/L; reference level, >0.16 g/L). Test for antineutrophil cytoplasmic antibodies (initially performed to exclude systemic vasculitis in view of the multisystem involvement) gave positive perinuclear pattern, but anti-myeloperoxidase antibodies were absent. Lupus anticoagulant and anti-cardiolipin antibody were absent, and the direct Coombs test gave a positive result. A diagnosis of SLE was made, with an SLE disease activity index (SLEDAI) of 30. The patient was given three doses of intravenous methylprednisolone 30 mg/kg every other day. The platelet count subsequently increased to 160 x 10^9 /L.

Renal biopsy was performed 10 days after admission and showed active proliferative glomerulonephritis, by way of mesangial and endocapillary proliferation with leukocyte exudation. Among the 35 glomeruli observed, one glomerulus showed a segmented cellular crescent.

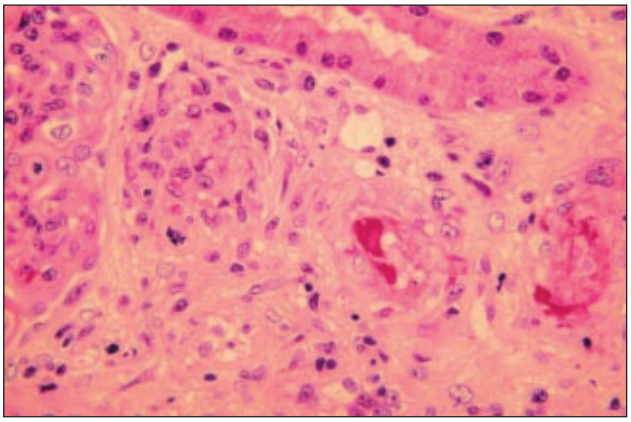

Fig. Photomicrograph of glomerulus showing moderate endocapillary proliferation with obliteration of capillary loops by leukocytes (H&E, x500)
The afferent arteriole is occluded by brightly eosinophilic material suggestive of fibrin

Karyorrhexis, wire-loops, and necrotising lesions were visible in foci. The capillary loops were much thickened, and silver staining revealed epithelial spikes and some tramline lesions. The most striking feature was the obliteration of some small arteries and arterioles by brightly eosinophilic material (Fig), which was confirmed by fibrin staining using Martius scarlet blue. Immunofluorescent staining showed a classic 'full-house' pattern at the mesangium and peripheral capillary loops, indicating active lupus nephritis class IV, according to the World Health Organization (WHO) nomenclature and lupus vasculopathy. The patient was given oral prednisolone 2 mg/kg and cyclophosphamide 2.5 mg/kg daily. The serum creatinine level subsequently decreased to 165 μmol/L, and C3 and C4 levels also showed an increasing trend.

Despite medical treatment, the patient had persistent hypertension, with a blood pressure of 140-150/90-100 mm Hg, which required intravenous labetalol and nifedipine for management. Severe anaemia (haemoglobin level, 50-80 g/L) and thrombocytopenia (platelet count, 50 x 10^9 /L) persisted. Smear analysis of peripheral blood showed features of intravascular haemolysis with fragmented red blood cells and schistocytes. The direct Coombs test gave negative results. Three weeks after admission, oliguria developed, the serum creatinine concentration increased to 314 μmol/L, and the serum lactate dehydrogenase concentration increased to 1200 U/L (reference range, 50-200 U/L). These clinical features were suggestive of TTP complicating SLE. A review of the renal biopsy specimen confirmed the presence of thrombotic microangiopathy.

The patient received three more doses of methylprednisolone and intravenous cyclophosphamide, and she underwent plasmapheresis consisting of a total of 14 daily exchanges at 1.5 times the plasma volume using cryoprecipitant-reduced fresh frozen plasma as replacement fluid. She also required a brief period of haemofiltration

Table 1. Causes of thrombotic microangiopathy in the setting of systemic lupus erythematosus (SLE)

	Thrombotic thrombocytopenic purpura related to SLE or cyclosporine use	Catastrophic antiphospholipid antibody syndrome	Fulminant lupus flare	Disseminated intravascular coagulation
Anaemia	Microangiopathic haemolytic anaemia	Immune-mediated (Coombs test positive)	Immune-mediated (Coombs test positive)	Microangiopathic haemolytic anaemia
Thrombocytopenia	Consumptive	Immune-mediated	Immune-mediated	Consumptive
Coagulopathy	Normal or slightly prolonged prothrombin and activated partial thromboplastin times	Normal prothrombin time; prolonged activated partial thromboplastin time	Normal	Increased prothrombin and activated partial thromboplastin times; low fibrinogen levels; high levels of fibrin degradation products
Bleeding tendency	Present	Absent	Present	Severe
Other features	Precipitating cause—cyclosporine, tacrolimus, ticlopidine; histologically small vessel thrombi without vasculitis	Livido reticularis; positive lupus anticoagulant; positive anti-cardiolipin antibody	Vasculitis present clinically and histologically; positive for antinuclear and anti-DNA antibodies; low level of complement	Precipitating cause—severe systemic illness, eg sepsis

because of severe oliguria, which gradually resolved; hypertension also subsided. The erythrocyte sedimentation rate became lower than 10 mm/h (reference range, 0-20 mm/h), and serum C3 and C4 levels normalised. Titres of ANA and anti-DNA decreased, and the creatinine level fell to below 100 μmol/L during the next 4 weeks. The patient's clinical course during the next 4 weeks was very unsteady because of complications from SLE and the immunosuppressive therapy. Four weeks after admission, she had transient mental confusion attributed to cerebral SLE or TTP. After the second monthly dose of intravenous cyclophosphamide, she developed *Pneumocystis carinii* pneumonia, which initially required high-dose co-trimoxazole therapy, and then 21 days of proguanil and clindamycin because co-trimoxazole induced bone marrow suppression and reactivation TTP, which required a 3-week course of daily plasmapheresis. A further episode of *Pseudomonas* septicaemia also developed because of a femoral catheter infection, which resolved after meropenam therapy.

The patient's condition improved gradually after 10 weeks. Plasmapheresis was gradually discontinued without TTP relapsing. In view of the frequent infective complications, pulse cyclophosphamide therapy was stopped and changed to mycophenolate mofetil at a dose of 33 mg/kg per day. She also received prophylaxis with monthly pentamidine (for *Pneumocystis* infection) and daily oral fluconazole (for candidiasis). Apart from the development of *Herpes zoster*, the patient remained well. At 20 months after presentation, she was asymptomatic with an SLEDAI of 4. Her serum creatinine level was 60 μmol/L, and although she still had microscopic haematuria, proteinuria had decreased to 0.2 g/d, C3 and C4 levels were normal, and anti-DNA titres were negative.

Discussion

This patient had typical multisystem features of SLE, fulfilling seven of the 11 diagnostic criteria of the American College of Rheumatology.[6] The nephritic features suggested active proliferative and possibly crescentic nephritis, and pulse steroid therapy was promptly given. Despite initial improvement, there was later rapid renal deterioration, perhaps because of active lupus nephritis itself; however, other causes of renal failure must also be considered. When TTP was suspected because of simultaneous haemolysis and thrombocytopenia, it was mandatory to examine the peripheral blood smear. This showed fragmented red blood cells and schistocytes, thereby indicating microangiopathic haemolytic anaemia. Further laboratory tests confirmed the diagnosis of TTP, and intensive immunosuppresive therapy and plasmapheresis were then started. It is also important to differentiate the following causes of thrombotic microangiopathy in the setting of SLE because they require different treatment approaches: disseminated intravascular coagulation, catastrophic antiphospholipid antibody syndrome, TTP related to SLE or cyclosporine use, or fulminant lupus flare with vasculitis (Table 1).[7]

Thrombotic thrombocytopenic purpura is a well-recognised complication of SLE. In 1998, Musio et al[5] identified 41 case reports of SLE and TTP in the English medical literature, including six patients younger than 20 years. The TTP occurred before SLE onset in six patients, together with SLE onset in 30, and after SLE onset in five.[5] In our review of the English-language medical literature since 1968, we identified 20 other paediatric cases of TTP complicating SLE.[8-22] However, it is controversial how commonly SLE and TTP are associated. In their series of 103 adult patients with TTP, Porta et al[23] reported that only 3.8% had SLE. On the other hand, Levine and Shearn[24] found SLE features in 23% of their series of 147 adult patients with TTP.[24] In children, Brunner et al[10] identified in the English medical literature from 1975 to 1998 a total of 35 patients with childhood-onset TTP and 17 (49%) of them subsequently received diagnoses of definite or incipient SLE. Conversely, TTP features occurred in 28% of 50 adult patients with SLE in the report by Devinsky et al.[25] In

children, several large case series of children with SLE did not document TTP as a complication or associated feature.[26-28]

The clinical features of the 21 paediatric cases (including this one) documented so far are summarised in Table 2. They comprise 17 females and four males, with ages ranging from 10 to 19 years. As in our case, nine of these 21 patients had simultaneous onset of TTP and SLE. In four other patients, however, TTP occurred after a variable period of inactive SLE of 2 to 5 years, while it preceded the onset of SLE by 3 months to 5 years in the remaining eight patients.[8] Renal manifestations were present in 18 patients during the episodes of TTP, including nephrotic syndrome (n=4), acute renal failure (n=10), hypertension (n=7), and variable proteinuria and haematuria in others. Thus, the patient in our case had the typical presentation of nephrotic syndrome progressing to acute renal failure. Unlike previous reports, ours involved a patient with severe intractable hypertension, which probably reflects extensive small vessel thrombosis in the renal circulation. Neurological manifestations were present in 12 patients (seizures in eight, focal signs in seven, and mental confusion/drowsiness/stupor/coma in seven). Histological findings of the kidneys were available in 12 patients and, in addition to thrombotic microangiopathy, they revealed various degrees of lupus nephritis (WHO class IV in two autopsies and four biopsies, class III in two biopsies, class II in three, and class V in one). The sample size, however, is too small to allow the identification of any clinical predictors of poor outcome.

Recognising TTP in the setting of SLE is important, because the combination of conditions carries a worse prognosis than SLE alone. The overall mortality of 41 patients reviewed by Musio et al[5] (including both adults and children) was 34%. Of the 21 cases analysed in Table 2, only two patients died, resulting in a mortality of 10% among children. Whereas plasmapheresis is controversial even in severe SLE, early plasmapheresis is standard therapy for TTP.[29]

Table 2. Cases of systemic lupus erythematosus (SLE) and thrombotic thrombocytopenic purpura (TTP) in children younger than 19 years

Study (location)	Sex/age (years)/ ethnicity or race	Presenting features of TTP episodes*
Present case, 2003 (Hong Kong)	F/12/Chinese	Malar rash, oral ulcer, nephrotic syndrome, haematuria, hypertension, acute renal failure, mental confusion
Tsao et al, 2002[9] (Taiwan)	M/13/Chinese	Fever, jaundice, nephrotic syndrome, haematuria, proteinuria, acute renal failure
Taher et al, 2002[11] (Lebanon)	F/16/NA¶	Headache, coma, hemiparesis, seizure, malar rash
Sakarcan and Stallworth, 2001[8] (United States)	F/15/NA	Shock, status epilepticus, acute renal failure; jaundice
Brunner et al, 1999[10] (Canada)	F/11/Laotian	Fever, bleeding; hypertension, headache, abdominal pain, arthritis, proteinuria, haematuria
	F/15/Italian	Fever, generalised bleeding, aphasia, hemiparesis, stupor, proteinuria, haematuria
	F/14/Eastern European	Systemic upset, petechiae, aphasia, hemiparesis, haematuria, proteinuria
	F/10/Italian	Bleeding, arthralgia, rash, proteinuria, pericarditis, pleuritis
	F/16/Filipino	Fatigue, weight loss, bleeding, headache, blindness, uveitis, arthralgia, vasculitic rash
Perez-Sanchez et al, 1999[22] (Spain)	F/16/NA	Hypertension, proteinuria, haematuria, acute renal failure, papilloedema, seizure, confusion, fever
	M/17/NA	Malaise, headache, oedema, hypertension, haematuria, proteinuria, acute renal failure, melena, petechiae
Caramaschi et al, 1998[15] (Italy)	F/14/NA	Fever, malar rash, vasculitis, arthritis; proteinuria, acute renal failure
Myung et al, 1996[17] (Korea)	M/17/Korean	Fever, aphasia, hypertension, proteinuria, haematuria, acute renal failure, seizure, alopecia, oral ulcer
Bray et al, 1994[12] (United States)	F/18/black	Fever, generalised bleeding, haematuria, proteinuria
Hess et al, 1992[13] (United States)	F/19/NA	Fever, arthralgia, epistaxis, hypertension, proteinuria, acute renal failure, slurred speech, hemiplegia, seizure
Jonsson and Fink, 1990[14] (United States)	F/10/white	Fever, rash, bleeding, proteinuria, haematuria, arthritis
Gatenby et al,1981[20] (United States)	F/12/NA	Fever, proteinuria, drowsiness, photosensitive rash, vasculitis, nephrotic syndrome
Oen et al, 1980[21] (Canada)	F/17/NA	Malar rash, purpura, jaundice, abdominal pain, hypertension, haematuria, proteinuria, seizures, confusion, hemiparesis
Dekker et al, 1974[19] (United States)	M/17/NA	Generalised bleeding, seizures, confusion
Alpert, 1968[16] (United States)	F/16/white	Fever, arthralgia, skin and vaginal bleeding, seizures, nephrotic syndrome, acute renal failure, gangrene in right leg
Lusher et al, 1968[18] (United States)	F/14/white	Fever, generalised bleeding, jaundice, haematuria, proteinuria, acute renal failure, headache, stiff neck

* In addition to microangiopathic haemolytic anaemia
† WHO World Health Organization
‡ IVMP intravenous methylprednisolone
§ IVCPD intravenous cyclophosphamide
‖ PE plasma exchange
¶ NA not available
** IVIG intravenous immunoglobulin
†† CPD cyclophosphamide
‡‡ HD haemodialysis

The rationale for early plasmapheresis came from a recent understanding of the pathogenesis of TTP.[30] In idiopathic TTP, a defect in a metalloprotease (ADAMTS-13) causes the increased release of large multimers of von-Willebrand factors (vWF) from endothelial cells, which leads to adhesion and aggregation of platelets and hence microvascular thrombi. Such a defect may result from a mutation of the gene encoding ADAMTS-13 (as in familial recurrent TTP), or autoantibodies against ADAMTS-13 (as in acquired idiopathic TTP or ticlopidine-associated TTP). Similar mechanisms may operate in SLE-related TTP. An adult patient with concurrent SLE and TTP was reported to have anti-CD36 antibodies that react with CD36 protein on platelets and small-vessel endothelium, thereby causing vascular injury and thrombotic microangiopathy.[31] In another paediatric case, vWF-cleaving protease activity was reduced and an inhibitor to the protease was present during the acute phase of TTP.[32]

Thus, patients with idiopathic TTP are treated with either infusion of fresh frozen plasma (which replenishes the functional metalloprotease) or plasmapheresis (which removes autoantibodies and large vWF multimers and replaces the functional metalloprotease). Randomised controlled trials have shown better results with plasmapheresis.[4] Other medical treatments reported in uncontrolled trials include the use of prednisone, vincristine, intravenous immunoglobulins, antiplatelet and antithrombotic agents, and vitamin E. As a rescue therapy, splenectomy and bilateral nephrectomy have also been described.[33]

In SLE-related TTP, standard immunosuppression should be given to control SLE activity, and patients should also receive plasmapheresis with fresh frozen plasma, cryosupernatant, or solvent-detergent–treated plasma as replacement fluid. In the 21 paediatric cases identified, almost all patients received steroid treatment, whereas plasmapheresis were used in 15 cases, and cyclophosphamide was added in six.[8] An additional reminder is

Temporal relationship of SLE and TTP	Renal histology (apart from microangiopathy)	Treatment for the TTP episodes	Outcome
Concurrent	Biopsy: WHO† class IV	IVMP‡ + IVCPD§ + PE‖	Complete remission
Concurrent	Biopsy: WHO class IV	IVMP + IVCPD	Complete remission
Concurrent	NA	PE + oral prednisolone	Complete remission
Concurrent	Biopsy: WHO class IV	IVMP, IVCPD, then oral prednisolone	Complete remission
TTP preceded SLE by 4 mo	NA	PE + oral prednisolone	Complete remission
TTP preceded SLE by 18 mo	NA	PE + aspirin, persantin, hydroxychloroquine	Complete remission
TTP preceded SLE by 5 y	NA	IVIG**; PE; PE + oral prednisolone on successive relapses	Complete remission at 5 y
TTP preceded SLE by 3 y	Biopsy: WHO class II	PE + aspirin; intravenous + oral prednisolone; PE + IVMP on successive relapses	Complete remission
TTP preceded SLE by 4 mo	NA	PE + oral prednisolone	Complete remission
SLE preceded TTP by 3 y	NA	Prednisolone pulse + PE + IVCPD	Partial remission
Concurrent	Biopsy: WHO class IV	Prednisolone pulses + oral prednisolone + PE + IVCPD	Complete remission at 2 y
Concurrent	Autopsy: WHO class IV	PE, oral prednisolone	Died of pulmonary haemorrhage
TTP preceded SLE by 2 y	Biopsy: WHO class IV	Oral prednisolone + PE; then IVMP + CPD††+ PE	Complete remission
TTP preceded SLE by 3 mo	NA	Oral prednisolone + PE	Complete remission
Concurrent	NA	Oral prednisolone + IVCPD + PE + HD‡‡	Complete remission at 18 mo
Concurrent	Biopsy: WHO class IIB	Fresh frozen plasma + PE + oral prednisolone	Complete remission
TTP preceded SLE by 3 y	Biopsy: WHO class II	Aspirin, dipyridamole, oral prednisolone, then oral prednisolone	Complete remission
SLE preceded by 5 y	Biopsy: WHO class III	IVMP pulses + PE	Partial remission at 12 mo
SLE preceded TTP by 2 y	NA	Steroid and aspirin, exchange transfusion	Complete remission
SLE for 5 y, TTP as terminal event	Autopsy: WHO class IV	NA	Died (generalised thrombi and haemorrhage)
Concurrent	Biopsy: WHO class III	Heparin, intravenous + oral prednisolone	Partial remission

that despite thrombocytopenia, platelet infusion should not be given to patients who are suspected to have TTP, because doing so will aggravate the microvascular thrombosis.

In conclusion, we reported the 21st case of SLE-related TTP occurring in a child. Our case illustrates the importance of early recognition and differential diagnosis of thrombotic microangiopathy. Whereas plasmapheresis is not of proven benefit in cases of severe SLE, it is life-saving in SLE-related TTP and must be instituted early to avoid a poor outcome.

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