Thrombotic microangiopathy in patients with phosphatidylserine dependent antiprothrombin antibodies and antiphospholipid syndrome


Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Kon Y. MD; Atsumi Tatsuya, MD, PhD; Hagiwara H. MD; Furusaki A. MD, PhD; Kataoka H. MD, PhD; Horita T. MD, PhD; Yasuda S. MD, PhD; Amengual O. MD, PhD; Takao K. MD, PhD.

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Please address correspondence to:
Tatsuya Atsumi, MD, PhD, Department of Medicine II, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo 060-8638, Japan.

E-mail: at3tat@med.hokudai.ac.jp

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Abstract
Thrombotic microangiopathy (TMA) is a rare disorder characterized by microvascular thrombosis. TMA has been reported in patients with antiphospholipid antibodies and/or antiphospholipid syndrome but its pathogenesis is not clarified. We present two patients with TMA associated with IgG phosphatidylserine dependent antiprothrombin antibodies (aPS/PT).

Case 1: A 44-year-old Japanese female with systemic lupus erythematosus (SLE) and positive lupus anticoagulant (LA) was started on ticlopidine after having stroke. Four weeks later she developed TMA. IgG/M/A anticardiolipin antibodies (aCL) were negative, but strong positive IgG aPS/PT were detected.

Case 2: A 32-year-old Russian female with SLE was admitted because of hypertension, renal insufficiency and proteinuria at 14 weeks of pregnancy. She developed TMA after surgical abortion. IgG aPS/PT and LA were strongly positive but IgG/M/A aCL were negative. Neither case had von Willebrand factor cleaving protease (ADAMTS-13). TMA was associated with thrombophilia rather than insufficient ADAMTS-13. Both patients were successfully treated with a series of plasma exchange.

Introduction
The antiphospholipid syndrome (APS) is a clinical disorder defined by recurrent thrombosis together with an adverse pregnancy history and the persistent presence of antiphospholipid antibodies (aPL) (1). Stroke and deep vein thrombosis are the most common clinical manifestations but a variety of thrombotic events have been reported in patients with APS (2).

Thrombotic microangiopathy (TMA) is a life-threatening condition related to the presence of localized or diffuse microvascular thrombosis. TMA is characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, neurological signs and renal involvement. The typical histopathological finding is hyaline thrombi composed of fibrin and platelets that occlude the microvasculature resulting in tissue ischemia.

Case reports
Patient 1.
A 44-year-old Japanese woman was admitted to our hospital in October 2002 with high fever and thrombocytopenia. Her previous medical history included the diagnosis of SLE in December 1980 based on thrombocytopenia, proteinuria, pleuritis, positivity for anti-DNA and for antinuclear antibody (ANA). At that time, her renal biopsy showed class IV lupus nephritis and she was treated with 60mg/day of prednisolone.

In December 1987, she had a lupus flare...
with psychiatric manifestations and was treated with steroid pulse therapy. In 1997, she developed thrombosis of the superior mesenteric artery with melena and progressive psychosis. Brain Magnetic Resonance Imaging (MRI) showed multiple lacunar infarcts and laboratory investigations revealed positive lupus anticoagulant (LA) and high titres of IgG aPS/PT. IgG/M anticardiolipin antibodies (aCL) were negative. Owing to all those findings, a diagnosis of APS was made and she was treated with aspirin and warfarin.

In September 2002, brain MRI showed massive lacunar infarcts despite adding 5 years of antithrombotic therapy, and ticlopidine to her treatment. One month later she developed thrombocytopenia (55 X 10^9/L) with high fever and was admitted to our department. On admission, the patient had a fever of 39°C, but she had neither skin manifestation nor lymphadenopathy. Laboratory studies demonstrated haemoglobin 9.6g/dl, white blood cell count (WBC) 3,700/μl, total bilirubin 0.6mg/dl, serum creatinine 1.5mg/dl, lactate dehydrogenase (LDH) 852 U/l (normal range 80–235 U/l) and positive ANA (1:640). Complement levels, anti-DNA antibody, fibrinogen and D-Dimer were within normal range. Serum haptoglobin level was low at 4 mg/dl (normal range, 90-170 mg/dl) and the direct Coombs’ test was negative. LA and IgG/M aPS/PT were sustained positive and IgG/M/A aCL were not detected. The peripheral blood smear revealed schistocytosis (Fig. 1A). A bone-marrow aspirate demonstrated a normal number of megakaryocytes without haemophagocytosis. Plasma ADAMTS-13 activity was normal and ADAMTS-13 inhibiting antibodies were not present.

The patient was diagnosed TMA and ticlopidin was stopped. Treatment with corticosteroid therapy and plasma exchange was started (daily for one week, followed by every 48 hours for another week) with clinical/ laboratory improvement (Fig. 2A). She has been on remission since discharge.

**Patient 2**

A 32-year-old Russian Caucasian woman admitted our hospital in October...
2002 having hypertension, renal insufficiency and proteinuria at 14 weeks of pregnancy. In 1987, she was diagnosed SLE in Russia and her previous medical history included recurrent abortions. She visited Hokkaido University Hospital in 1993 for evaluation of ischemic necrosis of the 1st and 3rd left hand fingers. Laboratory investigations showed positive LA and brain MRI displayed cerebellar infarct. Based on those finding, she was diagnosed as APS and aspirin was administered.

On admission, in October 2002, therapy with intravenous heparin was started because of her past history of miscarriages. One month later, she underwent surgical abortion due to advancing renal insufficiency. One week after the surgical procedure, she developed rapidly progressive anaemia and thrombocytopenia with deterioration of renal function. Her conscious level was slightly reduced with no other neurological manifestations. Physical examination revealed purpura on legs and hypertension at 159/108 mmHg. Laboratory studies demonstrated haemoglobin 8.0g/dl, WBC 18,000 /μl, platelet count 33×10⁹/L, serum creatinine 2.6mg/dl, LDH 1,305 U/l and positive ANA at 1:80. Schistocytes were present on peripheral blood smears. A direct Coombs’ test was negative. Complements, anti-DNA antibody and markers of thrombin generation and fibrinolysis were within normal range. Serum haptoglobin was under detectable level. LA was strong for IgG and IgM aPS/PT but negative for IgG/M/A aCL. In the two patients, LA and ADAMTS-13 inhibitor were evaluated as described elsewhere.

Clinical and laboratory manifestations of the patients are summarized in the Table. Both patients had typical clinical features of APS and were strongly positive for LA and aPS/PT, but negative for IgG/M aCL. In the two patients, ADAMTS-13 activity was normal and ADAMTS-13 inhibiting antibodies were not detected. Administration of ticlopidine triggered TMA in the first case and pregnancy, and/or surgical abortion was the trigger in the second patient.

**Discussion**

Antibodies against phosphatidylserine-prothrombin complex are members of the aPL family and responsible for many of the LA activities (16). Amongst antiprothrombin antibodies, aPS/PT were shown to be the most specific for the diagnosis of APS (13, 17). Several reports pointed out the relationship of TMA and APS (8), but ours is the first to show a possible association between TMA and aPS/PT in the absence of aCL.

Catastrophic APS represent an accelerated form of this syndrome with multiorgan failure and might have clinical and laboratory features similar to that found in patients with TMA. Catastrophic APS could be a possible diagnosis in our case 2, and it is likely that some patients diagnosed as TMA could be also included in the category of catastrophic APS.

Endothelial cell injury is a central phenomenon in the development of TMA. Endothelial cell damage increase the release of unusually large forms of vWF multimers and other prothrombotic agents, but decrease the release of prostaglandin I2, a strong inhibitor of platelet aggregation. Those unusually large vWF multimers are physiologically cleaved by the plasma metalloproteinase ADAMTS-13. The role of ADAMTS-13 in TMA is not clear, but it may be involved in the pathogenesis of TMA.

**Methods and results**

Antiphospholipid antibody profiles, ADAMTS-13 activity and ADAMTS-13 inhibiting antibodies were investigated. Anticardiolipin antibodies (IgG/IgM/IgA) were determined according to the standard ELISA (12), and aPS/PT (IgG/IgM) were assayed by in-house ELISA using the phosphatidylserine/prothrombin complex as antigen (13). For the detection of LA, the guidelines recommended by the Subcommittee for Standardization of the International Society of Thrombosis and Haemostasis were followed (14). Plasma ADAMTS-13 activity and ADAMTS-13 inhibitor were evaluated as described elsewhere (15).
ase ADAMTS-13. A severe deficiency in ADAMTS-13 regarded as highly specific for TTP (18-20). The lack of ADAMTS-13 activity may be congenital or acquired due to inhibitory IgG antibodies (21, 22).

Espinosa et al. (11) performed a computer assisted review of the literature to analyze the clinical and laboratory features of patients with TMA and aPL from 1983 to 2003 and suggested the association of TMA and aCL and/or LA. Amoura et al. (10) evaluated ADAMTS-13 in two patients with primary APS and TMA. A severe decrease in ADAMTS-13 activity and ADAMTS-13 inhibiting antibodies confirmed their diagnosis as TTP. On the other hand, in a recent report, Sato et al. found that none of patients with TTP secondary to connective tissue diseases had a severely decreased ADAMTS-13 activity, suggesting that the pathogenesis of TTP secondary to connective tissue diseases might be different than that of classical TTP (23).

In our cases, ADAMTS-13 activity was normal and ADAMTS-13 inhibiting antibodies were undetectable, suggesting that rather than TTP, other underlying cause should be responsible for the microvascular thrombosis (24). In APS, it is likely that several factors, including aPL/APS, lead to microvascular endothelial cell apoptosis as an initial insult, followed by platelet thrombus formations. Therefore the etiology of TMA in patients with aPL/APS is heterogeneous.

In conclusion, TMA is a rare condition in patients with APS but should be recognized as a life-threatening complication. Early and adequate management is essential. Further studies are needed to determine the relationship of aPL and the development of TMA in APS.

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References


