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Case report

Elevated levels of antibodies against phosphatidylserine/prothrombin complex and/or cardiolipin associated with infection and recurrent purpura in a child: a forme fruste of antiphospholipid syndrome?

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Abstract

Antiphospholipid syndrome is an autoimmune disorder characterized by the occurrence of venous and arterial thrombosis, as well as morbidity in pregnancy, in the presence of anti-phospholipid antibodies. The diagnosis of antiphospholipid syndrome is usually established based on clinical and laboratory findings by strictly following the 2006 Sapporo classification. However, the diagnosis remains challenging owing to the ongoing debates on the serological criteria. We report a case we describe as forme fruste antiphospholipid syndrome in which these criteria were not fulfilled. Purpura appeared repeatedly in a female infant starting from the age of 6 months and following episodes of upper respiratory infections and vaccinations. The levels of anti-cardiolipin IgG antibodies and anti-phosphatidylserine/prothrombin complex antibodies were elevated in accordance with these events. Histopathological evaluation revealed multiple small vessel thrombi in the dermis and adipose tissue. After 2 weeks of treatment with aspirin and heparin, the cutaneous symptoms subsided. Infection has long been associated with antiphospholipid syndrome, and anti-phosphatidylserine/prothrombin antibodies are considered a new marker for the diagnosis of antiphospholipid syndrome. Forme fruste antiphospholipid syndrome should be considered even if the antiphospholipid syndrome diagnostic criteria are not completely fulfilled, especially in the presence of elevated levels of anti-phosphatidylserine/prothrombin antibodies and known preceding infections.

Keywords: antiphospholipid syndrome, infection, infant, anti-phosphatidylserine/prothrombin antibodies

Introduction

Antiphospholipid syndrome is an autoimmune disorder characterized by the occurrence of venous and arterial thrombosis, as well as morbidity in pregnancy (abortions, fetal deaths, and premature births), in the presence of antiphospholipid antibodies [1].

Antiphospholipid syndrome is currently diagnosed on the basis of the 2006 Sydney update of the Sapporo classification [2]. To establish the diagnosis, at least one clinical manifestation of vascular thrombosis or pregnancy morbidity should be present, along with positive test results for circulating anti-phospholipid antibodies (anti-cardiolipin antibodies, anti-cardiolipin β 2 glycoprotein-I

antibodies, and lupus anticoagulant antibodies) recorded at least twice within 12 weeks. Incomplete fulfillment of the corresponding classification criteria, however, does not exclude the possibility of antiphospholipid syndrome [3]. The debates regarding the appropriate criteria, especially with respect to antibody titers in the serum, are ongoing. This makes establishing the diagnosis of antiphospholipid syndrome challenging. Furthermore, cases that may be designated forme fruste antiphospholipid syndrome have not been reported.

Herein we report a case of an infant with suspected forme fruste antiphospholipid syndrome following infection. We detected elevated titers of anti-cardiolipin and anti-phosphatidylserine/prothrombin complex antibodies. Infection long known to be associated with antiphospholipid syndrome may have triggered the occurrence of the symptoms and production of the antibodies, which are considered a new marker for antiphospholipid syndrome [4–6].

Case synopsis

The patient is a 2-year-old girl who developed purpura following a 38°C fever and lymphadenopathy of several cervical lymph nodes. She is the younger of identical twins. Purpuric macules were scattered on her cheeks and forearm; livedo reticularis was apparent on the lower legs (Figure 1 A,B). She was referred to our department for evaluation.

She had developed skin lesions previously in response to upper respiratory infections and vaccinations (MR: mumps and rubella) beginning at the age of 6 months. Purpura emerged approximately 1 week after the occurrence of systemic infection symptoms such as fever, cough, and rhinorrhea. At 7 months old, severe purpuric skin lesions and blood-filled blisters occurred (Figure 1 C,D). Antiphospholipid syndrome was suspected during the previous hospital visit and treatment with aspirin (5 mg/kg/day) was administered. Her eruptions ceased in less than a week.

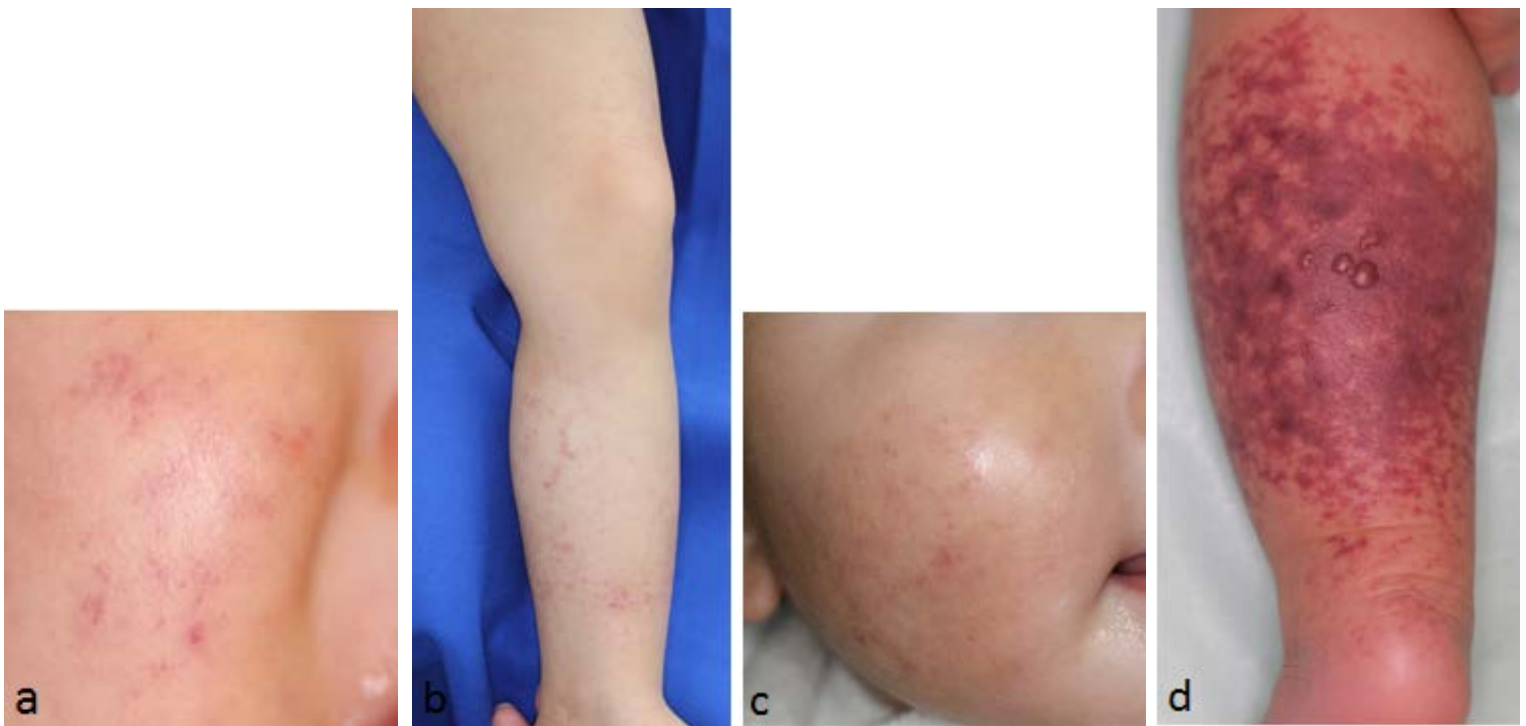


Figure 1. Skin manifestations accompanying infections. 1A. Purpura scattered on the cheeks at 2 years old. 1B. Purpura and livedo reticularis apparent on the left lower leg at 2 years old. 1C. Purpura scattered on the cheeks at 7 months old. 1D. Purpura and bloody blisters present on the left lower leg at 7 months old

Laboratory data obtained at our department showed leukocytosis (total leukocyte count: 22,600/mm³, reference range: 4,000–8,000/mm³), elevated level of C-reactive protein (0.90 mg/dl, reference range: ≤0.3 mg/dl), and reduced platelet count (150,000/mm³, reference range: 200,000–400,000/mm³). Antithrombin III (ATIII) (120.2%, reference range: 80–120%), thrombin-antithrombin complex (TAT) (4.9 µg/l, reference range: ≤3.0 µg/l), and glutamic-oxaloacetic transaminase (GOT) liver enzyme (50 IU/L, reference range: 10–28 IU/L) levels were elevated. The levels of Epstein–Barr virus viral-capsid antigen antibodies, including anti-viral capsid antigen IgM and anti-viral capsid antigen IgG, were also increased (anti-viral capsid antigen IgM: 20 x normal level, anti-viral capsid antigen IgG: 80 x normal level). Additionally, both anti-cardiolipin antibodies (10 U/ml, reference range: <10 U/ml) and anti-phosphatidylserine/prothrombin antibodies (13 U/l, reference range: <5 U/l) were elevated. Lupus anticoagulant antibodies and anti-cardiolipin β2 glycoprotein-I, anti-nuclear, and anti-double stranded DNA antibodies were all

negative. Protein C and protein S activity levels were normal. Brain MRI and abdominal ultrasonography revealed no abnormal findings.

Histopathology of the purpura on the lower leg showed multiple thrombi in the venules, arterioles, and small arteries throughout the dermis and adipose tissue (Figure 2).

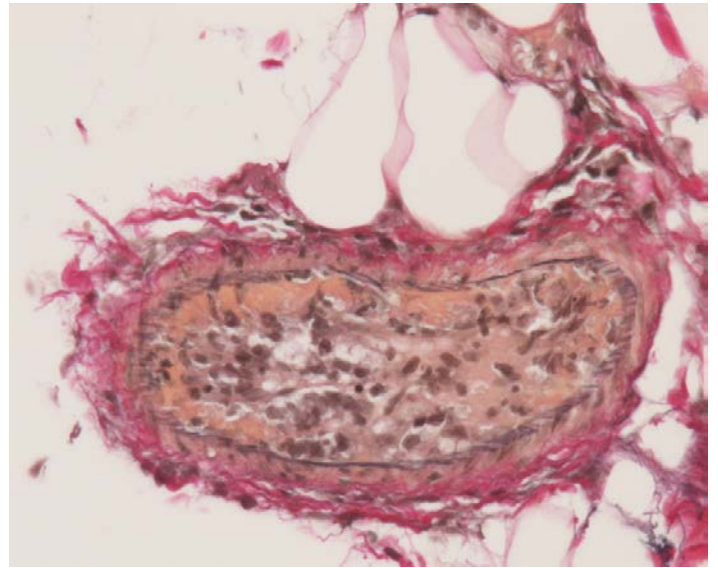
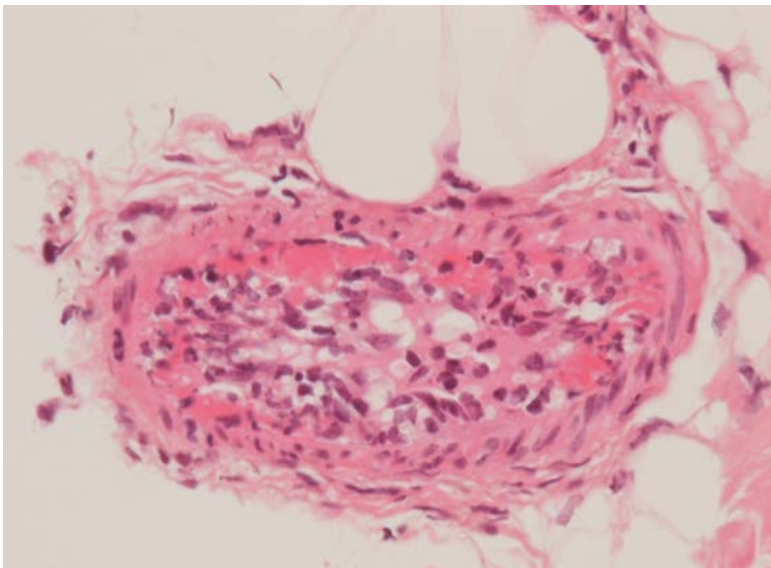
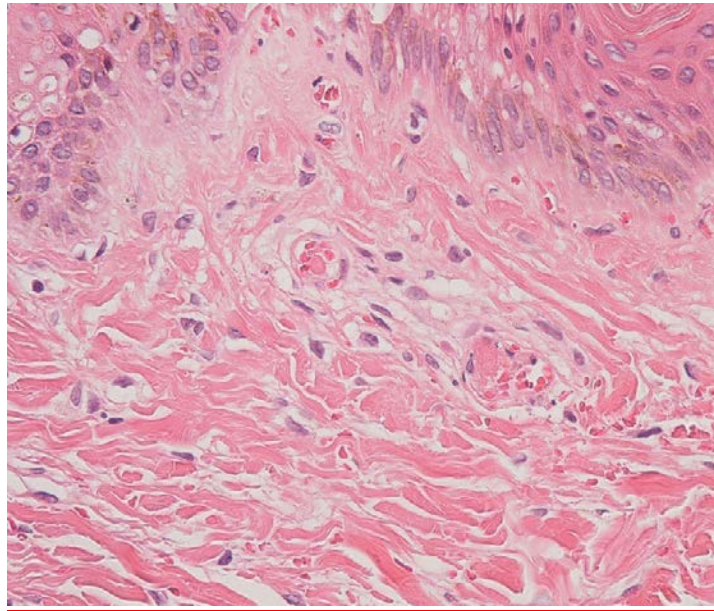


Figure 2. Histopathology of a purpuric lesion from the lower leg. A. Multiple thrombosis and extravasated red blood cells are present in small vessels in the upper and middle dermis.. B,C. Fibrin thrombosis with inflammatory cell infiltration is present in the small artery in the junction of the dermis and adipose tissue. The inflammatory cells include neutrophils, lymphocytes, and histiocytes. There is no destruction of the elastic lamina.

Therapy with aspirin (5 mg/kg/day) and low molecular weight heparin (800 U/day) was initiated. Her cutaneous symptoms improved after 2 weeks. No symptoms were observed during the follow-ups in the period of nearly 3 months. However, at 2 years and 4 months old, purpura reappeared following an episode of common cold.

Discussion

In light of the recently reported cases of antiphospholipid syndrome with characteristic clinical presentation, but no anticardiolipin antibodies, anti-cardiolipin β 2 glycoprotein-I antibodies, or lupus anticoagulant present in the serum, the current diagnostic criteria seem to need some revision [3, 7]. Although the results of the laboratory evaluation, in particular, barely elevated levels of anti-cardiolipin antibodies, did not completely fulfill the 2006 Sydney update of the Sapporo classification [2], we diagnosed our patient with antiphospholipid syndrome based on the increased levels of anti-phosphatidylserine/prothrombin antibodies, which are considered a promising marker for antiphospholipid syndrome [6]. In addition, we surmise that infection was a cause of the

observed pathology. In support of this notion, infection preceded the appearance of the skin lesions and elevation of the anti-phospholipid antibodies levels (Figure 3). Furthermore, Epstein-Barr virus infection preceded the occurrence of similar symptoms at 2 years old. The combination of the elevated titers of anti-phosphatidylserine/prothrombin antibodies, characteristic clinical presentation, and strong association of symptom appearance to infection was instrumental in establishing the diagnosis of forme fruste antiphospholipid syndrome.

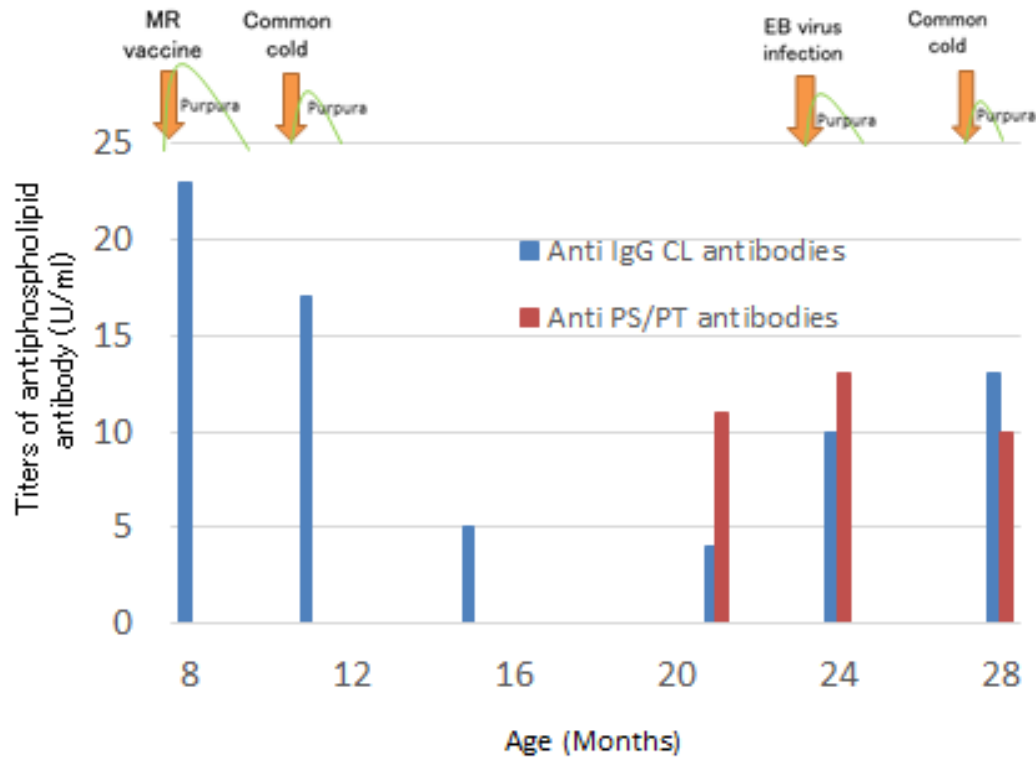


Figure 3. The relationship between anti-cardiolipin (CL) and anti-phosphatidylserine/prothrombin complex (PS/PT) antibodies titers and episodes of infections and skin eruptions. Skin lesions including purpura emerged at least 3 times during the period from 6 months old to 2 years old, each preceded by infections such as Epstein-Barr (EB) virus, common colds, and mumps and rubella (MR) vaccinations. The timing of the infective events suggests that infection played a role in the production of anti-phospholipid antibodies and perhaps in the pathogenesis of antiphospholipid syndrome.

Historically, viral, bacterial, and fungal infections have been reported to be associated with antiphospholipid syndrome. Viral infections, including Epstein-Barr virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, are most frequently documented. Furthermore, recent reports have described the elevation of the anti-phospholipid antibodies levels preceded by infections [4, 5], which was also observed in our case. This association suggests that infections may be involved in the pathogenesis of antiphospholipid syndrome, triggering the production of the antibodies and inducing the clinical symptoms. This is especially relevant in the case of catastrophic antiphospholipid syndrome, in which infection is the most common precipitating factor. Thus, 53% of catastrophic antiphospholipid syndrome patients experience such episodes [8].

Well known anti-phospholipid antibodies utilized for the diagnosis of antiphospholipid syndrome are lupus anticoagulant and anti-cardiolipin β 2 glycoprotein-I antibodies. Although these antibodies are directed against a phospholipid cardiolipin, various other antigens have been identified, including prothrombin. In particular, production of anti-phosphatidylserine/prothrombin antibodies is closely associated with the manifestations of antiphospholipid syndrome, positivity for lupus anticoagulant, and thrombotic events [6]. Because their sensitivity and specificity for antiphospholipid syndrome are higher than those of anti-cardiolipin antibodies, a high prevalence of the positivity for lupus anticoagulant and a decrease in the expression of blood coagulation factors have been reported in patients positive for anti-phosphatidylserine/prothrombin antibodies [1, 9]. Therefore, positivity for anti-phosphatidylserine/prothrombin antibodies may become a useful criterion for the diagnosis of antiphospholipid syndrome in the future [6].

Conclusion

In our patient, each of at least 3 episodes of purpura that occurred between the ages of 6 months and 2 years old was preceded by infection, including Epstein-Barr virus, common colds, and vaccinations. The timing of the infective events suggests that infection played a role in the production of anti-phospholipid antibodies and in the pathogenesis of the symptoms. We established the diagnosis of forme fruste antiphospholipid syndrome, which may develop into a complete form in the future. Our case suggests that even if the fulfillment of the antiphospholipid syndrome criteria is incomplete, a forme fruste of antiphospholipid syndrome should be considered if the symptoms and laboratory results indicate the possibility of this condition. The levels of anti-phosphatidylserine/prothrombin antibodies and the history of infections, which are strongly related to antiphospholipid syndrome, should be investigated to further support the diagnosis. Patients with forme fruste antiphospholipid syndrome should benefit from anticoagulant therapy. Since our case of antiphospholipid syndrome is not seronegative, continuous follow-up is important to investigate if the criteria for antiphospholipid syndrome will be fulfilled in the future.

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