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Case Report

A Case of Superior Mesenteric Artery Thrombosis Associated With Transient Elevation of Antiphospholipid Antibodies

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Transient elevation of antiphospholipid antibody (APLA) is commonly observed in cases of viral infection; however, it is generally not associated with clinical thromboembolic events. In this report, we present a rare case of superior mesenteric artery (SMA) thrombosis associated with a transient elevation of APLA and discuss its relationship with fibromuscular dysplasia and adenomyosis of the uterus. Furthermore, we discuss the use of anticoagulant therapy in cases with transient elevation of APLA. In this case, a 46-year-old woman with no significant medical history was diagnosed with intestinal stenosis after SMA thrombosis that had been resolved with anticoagulant therapy. Laboratory examination showed elevated levels of anticardiolipin antibody. Resection of the stenosed ileum and hysterectomy for huge adenomyosis were performed. Anticardiolipin antibody level normalized 4 months after the operation. Anticoagulant therapy was withdrawn after anticardiolipin antibody normalized, and the patient has been free from thromboembolic events ever since. Transient elevation of APLA should be kept in mind in all patients with thromboembolic events, including those with no medical history of collagen diseases or infection. In the present case, association with fibromuscular dysplasia and adenomyosis of the uterus is suspected, but further

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investigation is required. Once the APLA level normalizes with the resolved thrombus, decision of withdrawing the anticoagulant therapy can be considered.

Key words: Antiphospholipid antibody syndrome – Superior mesenteric artery – Thrombosis – Fibromuscular hyperplasia – Adenomyoma of the uterus

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thromboembolic complications, or recurrent pregnancy morbidity in the presence of persistently increased titers of antiphospholipid antibodies (APLA).[1] APS is usually observed in patients with collagen diseases such as systemic lupus erythematosus (SLE).[1] Furthermore, cases of viral infection have been reported to present with a transient elevation of APLA[2,3]; however, a transient elevation of APLA is not usually associated with clinical thromboembolic events.[4]

In this report, we present a case of superior mesenteric artery (SMA) thrombosis associated with a transient elevation of APLA and discuss its pathogenesis and treatment.

Case Report

A 46-year-old woman presented with a 3-month history of repeated diarrhea and abdominal pain related with her menstrual cycles. Her past medical history was unremarkable, with no indications of pregnancy-related morbidity. Computed tomography (CT), taken at admission to a referral hospital, revealed a thrombus in the proximal part of the SMA, edema in the ileum, and adenomyosis of the uterus (Fig. 1). The thrombus was resolved by administration of heparin for 3 weeks. She was readmitted to the hospital due to ileus on the day of discharge. A small intestinal series performed via a transnasal intestinal decompression tube demonstrated lead-pipe stenosis in the ileum. Her condition was complicated with sepsis from pharyngitis, and the sepsis aggravated despite removal of the decompression tube. She was transferred to our hospital for further treatment. On admission, a physical examination revealed a body temperature of 39.2°C, a pulse rate of 122/min, and a blood pressure of 118/50 mmHg. Her pharyngitis had resolved by this time. Laboratory examination was significant for thrombocytopenia (6.7×10^4 cells/mm^3; $13.0 \times 10^4 <$ normal $< 36.0 \times 10^4$ cells/mm^3), coagulopathy (prothrombin time 62.7%; normal, >80%; activated partial thromboplastin time 57.4 seconds; 25.5 seconds < normal < 40.5 seconds, fibrinogen 404 mg/dL; 250 < normal < 450 mg/dL), and elevated C-reactive protein level (5.0 mg/dL; normal, <0.3 mg/dL). Her white blood cell count was within the normal range (5900 cells/mm^3; $13.0 \times 10^4 <$ normal $< 36.0 \times 10^4$ cells/mm^3), but her neutrophil cell count was elevated (86.0%; 43.0% < normal < 78.0%). CT showed a slightly dilated ileum and adenomyosis of the uterus; however, neither SMA thrombosis nor inflammatory lesions were shown. The patient was administered heparin and imipenem/cilastatin. A bacterial culture of the arterial blood detected *Acinetobacter baumannii*. The patient had remittent fever every 4 days during the administration of antibiotics; however, the origin of the fever could not be identified. Bacterial translocation from the stenosis in the ileum was suspected. Further examination for coagulopathy was significant for a slightly decreased protein-C antigen level (64%; 70% < normal < 150%) and an elevated IgG anticardiolipin antibody level (>120 U/mL; normal, <10 U/mL). Immunologic examinations, including antinuclear antigen, anti–single-stranded DNA IgG

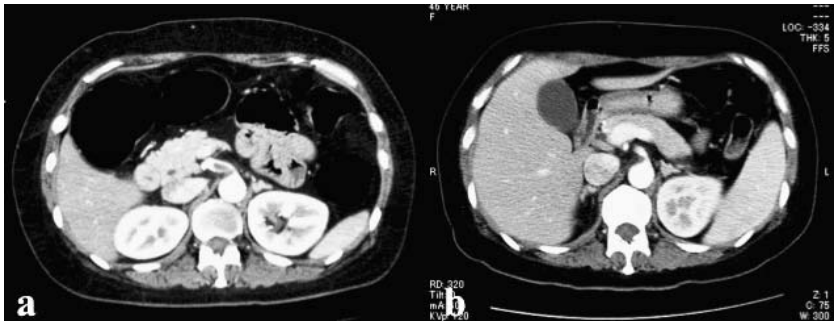

Fig. 1 CT showing a thrombus in the proximal portion of the SMA on first admission to the referral hospital (a). At the time of admission to our hospital, the thrombus had disappeared (b).

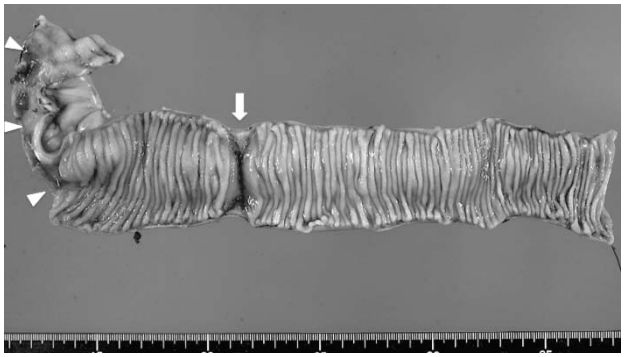

Fig. 2 The resected ileum showed diffuse stenosis (arrowheads) and a short stenotic segment (arrows).

antibody, anti–double-stranded DNA IgG antibody, anti-ribonucleoprotein antibody, and myeloperoxidase–anti-neutrophil cytoplasmic antibody, were not significant. Based on the elevated anticardiolipin antibody level and SMA thrombotic event, APS was considered the cause of the SMA thrombosis. CT did not demonstrate any occluded large branches of the SMA; however, thrombosis of the peripheral arteries could not be ruled out. Because the patient had a history of repeated diarrhea related to her menstrual cycles, external endometriosis in the ileum was among the differential diagnoses. We scheduled resection of the stenosed ileum and hysterectomy. After entering the peritoneal cavity through a midline laparotomy incision, a 10-cm-long constricted ileum was observed 25 cm from the terminal ileum. The constricted ileum adhered to the swollen uterus. Pulsation of the large branches of the ileocecal artery was palpable; however, that of the marginal artery close to the constricted lesion was vague. A 30-cm-long ileum, including stenosis, was resected. Thereafter, hysterectomy was performed. The resected ileum showed stenotic lesions with an ulcerative lesion (Fig. 2). Microscopically, the ulcerative lesion showed necrotic inflammatory granulation tissue, fibrosis of the submucosal layer, and foci of organized thrombi with neovascularization (Fig. 3a); however, there was no evidence of vasculitis. These findings were consistent with ischemic change. It was unclear whether thrombi were formed in the peripheral arteries, or if they were emboli from the thrombus at the proximal part of the SMA. In addition to the ischemic findings, irregular fibromuscular hyperplasia of the arterial wall was noted (Fig. 3b). The specimen of the uterus showed many ectopic islands of endometrial tissue, which was compatible with adenomyosis. Anticoagulant therapy with warfarin was started postoperatively. Anticardiolipin antibody levels had decreased to 15 U/mL 2 months after the operation and, finally, normalized 4 months after the operation. Anticoagulant therapy was discontinued 26 months after the operation. The postoperative course has been uneventful for 46 months without thrombotic events.

Discussion

APS is a clinical condition seen in patients with thromboembolic events or pregnancy morbidity and is often associated with collagen diseases such as SLE. The International Preliminary Classification (Sapporo criteria) of APS was formulated by an international consensus conference in 1999[1] and was subsequently updated in 2006 in Sydney.[5] The Sydney criteria defined APS as present if at least 1 of the clinical criteria (vascular thrombosis or pregnancy morbidity) and 1 of the laboratory criteria (elevation of lupus anticoagulant, anticardiolipin antibody of IgG and/or IgM isotype, or anti-β2 glycoprotein antibody of IgG and/or IgM isotype) are present on 2 or more occasions at least 12 weeks apart. Anticardiolipin antibody must be present in medium or high titers. The present patient was diagnosed with APS initially, and although IgG anticardiolipin antibody levels remained elevated, they were present in low titers 2

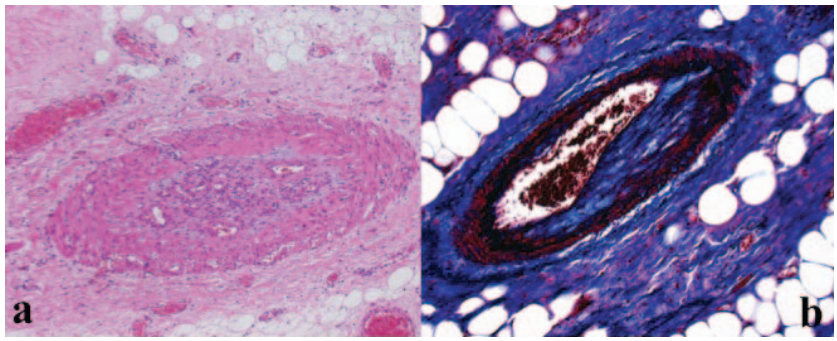

Fig. 3 Histopathologic examination of the arterial wall in the ileum showing foci of organized thrombi with neovascularization (a) [H&E (×100)], an irregular intimal fibromuscular hyperplasia of the arterial wall (b) [Masson's trichrome (×100)].

months after the operation. Because the IgG anticardiolipin antibody levels normalized 4 months after the operation, the patient did not meet the Sydney criteria. There have been case reports that used the term "transient APS," but we considered "transient elevation of APLA" to be more appropriate for the clinical condition observed in our patient. Transient elevation of APLA is often associated with viral infections such as hepatitis C virus, human immunodeficiency virus, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, adenovirus, and parvovirus B.[2,6] The pathogenesis of a transient elevation of APLA in the present patient was unclear. She had repeated episodes of diarrhea in accordance with her menstrual cycles, and the constricted ileum adhered to the swollen uterus. These findings suggest that the stenosis of the ileum, rather than a viral infection, was causing the diarrhea. The patient had a bacterial sepsis by bacterial translocation from the ulcerative lesion in the ileum; however, the SMA thrombosis had developed prior to the sepsis episode. Based on these clinical manifestations, we concluded that the SMA thrombosis was not associated with infectious events. Anticardiolipin antibody levels normalized after hysterectomy, suggesting that adenomyosis of the uterus may also have been a cause of the elevated anticardiolipin antibody levels. To date, there have been no reports describing a relationship between adenomyosis of the uterus and APS. Further investigation seems merited.

Thromboembolic events develop in a variety of organs in those with APS,[7] but they are rare in cases of a transient elevation of APLA.[4] Only a few cases of a transient elevation of APLA (including transient APS) developed thromboembolic events[2,3,8,9]; however, SMA is a rare target vessel in cases of a transient elevation of APLA.

Another interesting feature of the present case was the fibromuscular hyperplasia of the arteries in the ileum, as demonstrated by a pathologic examination. The pathologic features of APS consist of thrombotic microangiopathy and ischemia caused by arterial or venous thromboses. These features are not different from those of other thrombotic events.[7] Fibromuscular hyperplasia is classified as one of the subtypes of fibromuscular dysplasia (FMD).[10] FMD is a nonatherosclerotic and noninflammatory vascular disease that involves medium-to-small arteries, commonly the renal and carotid arteries, but rarely mesenteric arteries.[11] Little is known regarding the etiology of FMD. Associations with hormonal factors, vessel-wall ischemia owing to occlusion of the vasa vasorum by stretching, cigarette smoking, endocrine diseases, and congenital defects in the arterial walls have all been suggested.[12] The relationship between APS and FMD is unclear. Only 1 report has described FMD of the SMA in an APS case.[13] The renal and carotid arteries are commonly involved in FMD, and the SMA is a rarely affected site. In the present case, it may seem as if FMD contributed to the development of the arterial thrombi in the ileum; however, the large thrombus initially developed in the proximal part of the SMA, where no irregular segment suggestive of FMD was detected. Thus, we concluded that APLA, rather than FMD, was associated with the SMA thrombosis in the present patient. To our knowledge, there is no case of SMA thrombosis in a transient elevation of APLA except for the present case. This pathologic finding suggests that APLA levels may stay elevated over a period of time before the operation. Because the abdominal symptoms continued for 5 months before the measurement of APLA, APLA levels may have already been elevated at symptom onset. The specific nature of the association between APS and FMD will require additional investigation.

Management of APS is based on anticoagulant and immunosuppressive therapy. After thromboembolic events, intermediate-to-high intensity anticoagulant therapy with warfarin (international normalized ratio of 2.0 to 3.0 or more) reduced the rate of recurrent thrombosis.[14] Immunosuppressive therapy with steroids is limited to patients with catastrophic APS.[7] In this case, we initiated warfarin administration after the operation and continued it for 1 year. Although withdrawal of anticoagulant therapy increases the risk of recurrent thromboembolic events,[15] we stopped warfarin administration after the anticardiolipin antibody level normalized. No thromboembolic event developed thereafter, although close follow-up is considered necessary. In cases with a transient elevation of APLA, withdrawal of anticoagulant therapy may be acceptable when APLA normalizes and thrombus is resolved by anticoagulant therapy.

In conclusion, we have described a rare case of SMA thrombosis associated with a transient elevation of APLA. Association of adenomyosis of the uterus is suspected, but further investigation is necessary. Anticoagulant therapy is essential for thromboembolic events occurring during a transient APLA elevation, although it may be possible to withdraw anticoagulant therapy when the APLA level normalizes and thrombus is resolved by anticoagulant therapy.

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