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Takayasu Arteritis With Antiphosphatidylserine/Prothrombin Antibody-Positive Antiphospholipid Syndrome
Case Report and Literature Review
Shoichi Fukui, MD, Shogo Hirota, Naoki Iwamoto, MD, PhD, Hiroki Karata, MD, and Atsushi Kawakami, MD, PhD

Abstract: A relationship between Takayasu arteritis (TA) and positive antiphospholipid antibody states has been pointed out, but patients with TA complicated with antiphospholipid antibody syndrome (APS) are rare. Here we report the case of a 17-year-old Japanese man diagnosed with TA based on pulselessness of the left brachial artery, discrepancy of blood pressure between the upper extremities, and arterial wall thickening and narrowing of artery in contrast computed tomography. He was also diagnosed with provisional APS based on a pulmonary infarction without narrowing of the pulmonary artery and positive antiphosphatidylserine/prothrombin antibody. The patient also had concurrent Crohn’s disease (CD) based on histopathological findings, which may have been associated with TA. We started high-dose corticosteroid therapy and anticoagulation therapy, and his symptoms including fever, dizziness, chest pain, and lower-right uncomfortable abdomen improved.

We reviewed 9 cases of TA with APS including our patient by conducting a PubMed search. Based on past reports, we considered the relationship among TA, APS, and CD. Clinicians should bear in mind that many etiologies can exist in 1 patient, and differential diagnoses are essential.

INTRODUCTION
Takayasu arteritis (TA) is a rare large-vessel vasculitis variant that affects predominantly young women.\(^1\) TA affects the aorta and its main branches\(^2\) and the pulmonary arteries.\(^3\) TA is commonly seen in Japan, South East Asia, India, and Mexico.\(^4\) It was reported that 150 new TA cases occur each year in Japan,\(^5\) whereas the reported incidence of TA in Olmsted County, Minnesota, United States, was 2.6 new cases per year per million population.\(^6\)

Antiphospholipid syndrome (APS) is characterized by obstetric and thrombotic complications in the presence of antiphospholipid antibodies, which consist of anticardiolipin antibody (aCL), lupus anticoagulant (LA), and anti-\(β_2\) glycoprotein I (\(β_2\)GPI). In addition, antiphosphatidylserine/prothrombin antibody (APS/PT) was revealed to be associated with APS.\(^7\) An association between TA and APS has rarely been described. Here we report a case of TA associated with APS with positive APS/PT.

CASE PRESENTATION
A 17-year-old Japanese man was admitted to our hospital complaining of body weight loss and fever. The weight loss began 6 months prior to this admission, amounting to a 15 kg reduction as of the admission. Four months prior to this admission, he began feeling general fatigue and dizziness when he changed the position of his head. Three months prior to the admission, he experienced instant chest pain on the left side when he breathed to the maximal inspiratory level, which had nothing to do with the time of day, and his lower right abdomen felt uncomfortable (which was a heavy feeling but not pain) in the lower right abdomen that had nothing to do with his meal intake. He did not have any symptoms such as changes in bowel habits, diarrhea, constipation, and hematochezia. Two weeks before his admission, the fever emerged. He did not have any notable medical history.

His physical examination on admission revealed the following: body temperature 37.5°C; blood pressure, right arm 112/68 mm Hg, left arm could not be measured; pulse rate 90/min, and respiratory rate 16/min. Auscultation of the chest showed no heart murmur or crackles. Pulses of the left brachial and radial arteries were not palpable. There were no skin eruptions.

His laboratory test results were as follows: white blood cell (WBC) count 10,300/μL (neutrophils 75%, lymphocytes 22%, monocytes 3%, eosinophils 0%, and basophils 0%); hemoglobin 10.8 g/dL; platelets 466,000/μL; C-reactive protein (CRP) 16.6 mg/dL (normal range <0.3 mg/dL); erythrocyte sedimentation rate (ESR) 87 mm/h (normal range 1–10 mm/h); serum creatinine (Cr) 0.56 mg/dL (normal values <1.0 mg/dL). He had a prolonged activated partial thromboplastin time (APTT) (60.3 s, normal range: 24.3–36.0 s), and elevated D-dimer (1.2 μg/mL, normal values <1.0 μg/mL). All of the following were negative: aCL (by enzyme-linked immunosorbent assay
(ELISA), LA (by diluted Russell’s viper venom time test), and aβ2GP I (by ELISA). Antiphosphatidylserine/prothrombin antibody (aPS/PT) (IgG, by ELISA) was positive (18 U/mL, normal values <10 U/mL). Antinuclear antibody was negative. Human leukocyte antigen (HLA) typing was *B15:0101*/*B52:0101. A urinalysis did not show any remarkable data.

Contrast computed tomography (CT) showed arterial wall thickening of the ascending and descending aorta and narrowing of the left subclavian artery. Positron emission tomography (PET) showed 18F-fluoro-2-deoxy-D-glucose (FDG) accumulation in the wall of the left subclavian artery. A defect of contrast in the pulmonary artery without narrowing suggested pulmonary thrombosis (Fig. 1A). PET showed no FDG accumulation in the wall of the same lesion of the pulmonary artery (Fig. 1B).

In the patient’s left lung, subpleural wedge-shaped consolidation was observed in the area that was perfused by the obstructed pulmonary artery (Fig. 2). Ventilation perfusion lung scintigraphy showed a mismatch of perfusion and air in the left lung (Fig. 3). PET also showed FDG collection in the ileocecum (Fig. 4A). Colonoscopy showed redness of mucus of the ileocecum (Fig. 4B). The biopsy specimen of the ileocecum showed a noncaseating epithelioid granuloma (Fig. 5).

The patient’s findings fulfilled the following criteria issued by the American College of Rheumatology 1990 for the classification of TA:6; age at disease onset <40 years, decreased brachial artery pulse, blood pressure difference >10 mm Hg, and arteriogram abnormality, and we therefore diagnosed TA. We suspected that the dizziness experienced by the patient when he changed the position of his head was induced by subclavian steal blood syndrome, because his left subclavian artery was severely narrowed. Because the patient also had a pulmonary embolism, an infarction without narrowing of the pulmonary artery, and positive aPS/PT, we diagnosed provisional APS pending a confirmatory lab result. In addition, based on the histopathological findings of the ileocecum, we also diagnosed Crohn’s disease (CD).

We started 50 mg prednisolone per day and anticoagulant therapy by warfarin. The patient’s fever and chest pain when he breathed then disappeared quickly. His CRP level and ESR declined. One month after the initiation of treatment, CT showed a partial recanalization of the previously occluded left subclavian artery. Sixteen weeks after the initiation of treatment, antiphosphatidylserine antibody was also positive (12 U/mL). We made a diagnosis of provisional APS with positive aPS/PT. A new pulmonary embolism did not occur during the subsequent 1 year of follow-up. His left lower abdominal discomfort never emerged again.

**DISCUSSION**

We have reported a case of TA associated with APS with positive aPS/PT. Our patient’s case had 2 characteristic features: TA complicated with APS, and CD. Regarding the complication of APS, 2 problems hamper the diagnosis of APS. One is that the classification criteria for definite APS (ie, the Sapporo criteria)9 do not include aPS/PT as a specific antibody for APS. It is now acknowledged that APS can exist in the presence of autoantibodies other than aCL, LA, and aβ2GPI.
We searched for the existing case reports of TA associated with APS by conducting a PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) without a date, using the search terms “Takayasu arteritis” and “antiphospholipid antibody syndrome.” We found 8 cases of TA with APS other than our patient (Table 1). We found 1 definite APS (classified by Sapporo criteria) patient and 2 other patients with clinical and serological features of APS (insufficient to satisfy the Sapporo criteria) in a report by Jordan et al, but the detailed clinical history of these 3 patients was not available and thus we excluded them. We also excluded patients with solely positive antiphospholipid antibodies without thrombotic events (ie, arterial thrombosis, venous thrombosis, or pregnancy loss).

As shown in the table, of the 9 cases (including our patient), 7 patients had aCL and 7 patients had LA. Only 1 patient had positive a2B2GP I. APS/PT was not checked in any of the cases shown in the table except for our patient. To our knowledge, this is the first case report of a TA patient with APS who had positive aPS/PT. Two of the 9 patients (including our case) were men. Three patients had undergone an abortion. Deep vein thrombosis was seen in 2 patients. One patient’s case was complicated with systemic lupus erythematosus (SLE). Although in SLE cases, small-vessel involvement is the most frequent, medium- and large-vessel vasculitis may present with visceral affection. It was therefore difficult to distinguish TA from large-vessel vasculitis of SLE in the case reported by Caso et al.

Our patient also had CD. Reny et al reported that 9% of 44 TA patients had CD. Although the pathogeneses of both TA and CD are unclear, some similarities have been pointed out. The fact that both TA and CD show granulomatous changes histopathologically may affect this high concurrence ratio. In addition, tumor necrosis factor-alpha (TNF-α) monoclonal antibody is effective for both TA and CD, which may suggest the presence of a common inflammatory pathway in both diseases.

On the other hand, Kraiem et al reported that some antiphospholipid antibodies were positive in 54.2% of 48 CD patients. Sipeki et al reported that of 264 CD patients, aPS/PT was positive in 20.4% (any 1 of IgG, IgM, or IgA) and that 14.6% of the CD patients without events of thrombosis had positive aPS/PT, whereas 50.0%, 36.4%, or 40.0% of the CD patients with events of arterial thrombosis, venous thrombosis, or pregnancy loss had positive aPS/PT, respectively.

Bacterial translocation (as one of the causes of the production of autoantibodies) is thought to induce autoantibodies in inflammatory bowel disease. Similarly, bacterial translocation may be associated with the production of aPS/PT in CD patients. Although it is not general practice to measure antiphospholipid antibodies when diagnosing CD, there are many more CD patients with positive antiphospholipid antibodies than we expected. Measuring antiphospholipid antibodies in CD patients may be important to determine the prognosis regarding thrombosis.

Although the relationships among TA, APS, and CD in our patient are unclear, autoantibodies, the formation of granuloma, and bacterial involvement may have been associated with his case’s etiology.

In conclusion, we have reported the case of a young adult patient with TA complicated with APS, which is very rare. Clinicians should bear in mind that many etiologies can exist in 1 patient and that differential diagnoses are essential. Further studies of TA and APS regarding clinical and prognostic differences are needed.
### TABLE 1. Nine Cases of Takayasu Arteritis (TA) With Antiphospholipid Syndrome (APS)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Age, Sex</th>
<th>History</th>
<th>Symptoms</th>
<th>Complication</th>
<th>Affected Artery</th>
<th>Autoantibody</th>
<th>APTT</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caso, 2002¹⁷</td>
<td>36,F</td>
<td>Abortion, HTN, migraine, peripheral vascular disease, photosensitivity</td>
<td>HTN, Livedo reticularis, Lt. hemiparesis</td>
<td>SLE</td>
<td>Rt. CIA, Rt. ICA, Rt. RA, Lt. VA</td>
<td>aCL, ANA (1:160), Anti-dsDNA, LA</td>
<td>NA</td>
<td>PSL 75mg/day, warfarin, IVCY</td>
<td>Improved</td>
</tr>
<tr>
<td>Dhaon, 2011¹⁸</td>
<td>23,F</td>
<td>Abortion, pre-eclampsia</td>
<td>Dyspnea, pulselessness of Lt. upper limb</td>
<td>AR, MR, PH, Dilated myopathy</td>
<td>Ab Ao, CA, MA, Lt. AxA, Lt. SCA, Rt. CCA</td>
<td>aCL, aβ2GP I</td>
<td>NA</td>
<td>Warfarin</td>
<td>NA</td>
</tr>
<tr>
<td>Fain, 1995¹⁹</td>
<td>46,M</td>
<td>Bilateral adrenal hemorrhage, DVT</td>
<td>Abdominal and lumbar pain, Fever</td>
<td>(–)</td>
<td>IR Ao</td>
<td>aCL, LA</td>
<td>NA</td>
<td>PSL 1 mg/kg</td>
<td>Improved</td>
</tr>
<tr>
<td>Jishi, 2005²⁰</td>
<td>41,F</td>
<td>Dysarthria, erythematous skin lesion, Lt. carotid bruit, Lt. facial palsy, Lt. hemiparesis, Pins and needles sensation over Rt. hand, Pulselessness of Bi. radial pulse</td>
<td>AR, Cerebral infarction, MR, TR</td>
<td>(–)</td>
<td>AA, Bi. CCA, Bi. SCA</td>
<td>aCL, LA</td>
<td>APTT ratio: 1.4</td>
<td>Warfarin</td>
<td>Improved</td>
</tr>
<tr>
<td>Santiago, 2007²¹</td>
<td>33,F</td>
<td>Abortion, DVT, PE</td>
<td>Decreased brachial and radial pulses, pain and cyanosis of the Lt. upper limb, systolic murmur in Lt. infrarenal area</td>
<td>(–)</td>
<td>Lt. ITA, Lt. SCA, Lt. VA</td>
<td>aCL, LA</td>
<td>NA</td>
<td>PSL 1mg/kg, MTX 15mg/week, Anticoagulant–IFX</td>
<td>Improved</td>
</tr>
<tr>
<td>Yokoi, 1996²²</td>
<td>84,F</td>
<td>AMI, arthralgia, cerebellum infarction, dementia, fever, gait disturbance, gangrene, visual disturbance</td>
<td>Dyspnea, fatigue, fever</td>
<td>AR</td>
<td>As Ao, Bi. CCA, Bi. PA</td>
<td>aCL, ANA (1:390), LA</td>
<td>NA</td>
<td>Surgery for AR</td>
<td>Death (Sudden death)</td>
</tr>
<tr>
<td>Kaku, 2006²³</td>
<td>36,F</td>
<td>Chest pain, hemoptysis</td>
<td>Dizziness, fatigue, fever</td>
<td>(–)</td>
<td>Lt. PA, Th Ao</td>
<td>LA</td>
<td>42sec</td>
<td>PSL 30mg/day</td>
<td>Improved</td>
</tr>
<tr>
<td>Our case</td>
<td>17,M</td>
<td>(–)</td>
<td>Fatigue, fever, uncomfortable abdomen</td>
<td>(–)</td>
<td>CoM disease, PE, AA, Da Ao, Lt. SCA</td>
<td>aPS/PT</td>
<td>60sec</td>
<td>PSL 50mg/day</td>
<td>Improved</td>
</tr>
</tbody>
</table>

## Notes

The 8 previous cases were identified by a PubMed search using the search terms “Takayasu arteritis” and “antiphospholipid antibody syndrome,” with no date parameter. The 8 previous cases were identified by a PubMed search using the search terms “Takayasu arteritis” and “antiphospholipid antibody syndrome,” with no date parameter.
CONSENT
Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the editor of this journal.

REFERENCES
3. Pulmonary pulseless disease: pulmonary involvement in so-called Takayasu’s disease, Clinical Conference in Cardiology from the third medical division, Kyoto University Hospital, Kyoto, Japan, Chest 73, 1978, 651–657.