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【 CASE REPORT 】

A Non-smoking Woman with Anti-phospholipid Antibodies Proved to Have Thromboangiitis Obliterans

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Abstract:
A 48-year-old woman with severe pain and numbness of her right leg and foot was admitted to our hospital. She had never smoked and had little exposure to passive smoking. Initially, polyarteritis nodosa with anti-phospholipid antibodies was considered. Combination therapy with methylprednisolone pulse therapy, intravenous cyclophosphamide pulse therapy, vasodilators, antiplatelet agents, and anticoagulants was not effective. Vasculopathy was progressive, and she presented with gangrene of the toes. She required amputation of her right leg. The pathological findings of the amputated leg revealed thromboangiitis obliterans (TAO). TAO should be considered even in non-smoking women. Non-response to immunosuppressant and anticoagulant therapies may be a clue to the diagnosis of TAO.

Key words: anti-phospholipid antibodies, anti-phospholipid syndrome, Buerger's disease, non-smoking, polyarteritis nodosa, thromboangiitis obliterans

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Introduction

Thromboangiitis obliterans (TAO), also called Buerger's disease, is a nonatherosclerotic segmental inflammatory disease that affects the small and medium-sized arteries and veins in the upper and lower extremities (1). Affected patients are mostly young, with the usual age of onset less than 45-50 years, men, and chronic tobacco smokers who present with distal extremity ischemia, ischemic ulcers, or frank gangrene of the toes or fingers. The exclusion of other diseases such as autoimmune diseases, a hypercoagulable state, and diabetes mellitus, is required (2, 3). Anti-phospholipid syndrome shares the clinical characteristics of arterial thrombosis and recurrent thrombophlebitis with TAO (4). Pathologically, TAO in any stage is distinguishable from atherosclerosis and other vasculitis by the preservation of the internal elastic lamina (5).

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis predominantly targeting medium-sized arteries and not associated with glomerulonephritis or small vessel involvement. PAN affects patients of any sex, age, or ethnic background. The peak incidence occurs in the 5th and 6th decades of life (6). In middle-aged, non-smoking women with clinically and radiographically diagnosed medium-sized arteritis, TAO might be misdiagnosed as PAN if information on the histopathology of medium-sized arteries is not obtained. In addition, cases of non-smoking women with TAO with anti-phospholipid antibodies have been rarely reported.

We herein report the case of a non-smoking woman with PAN-like TAO. TAO might occur in non-smoking women or those who are passive smokers. The presence of anti-cardiolipin antibodies might have been associated with her poor prognosis. A pathological examination of her amputated leg led to the diagnosis in the present case.

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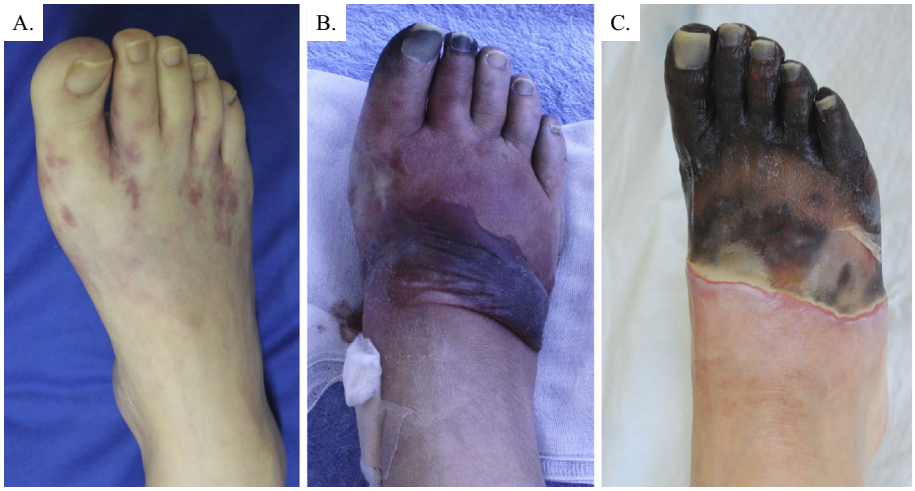


Figure 1. **Time course of the patient's right foot and toes. Ischemia increased, and gangrene appeared. A: On admission, B: One month after admission, C: Eighty days after admission.**

Case Report

A 48-year-old woman was admitted to our hospital with numbness of her right leg and foot. She had no history of recurrent abortion or strokes. She had never smoked, and she had little exposure to passive smoking. Three years before admission, erythema nodosa was diagnosed by a dermatologist, and she had been prescribed prednisolone (10 mg/day) for a short period. One month before admission, she developed numbness in her right lower leg and foot. Seven days before admission, non-palpable purpura appeared and progressed around her right toes accompanied by severe pain. She was treated with up to 20 mg/day prednisolone before admission.

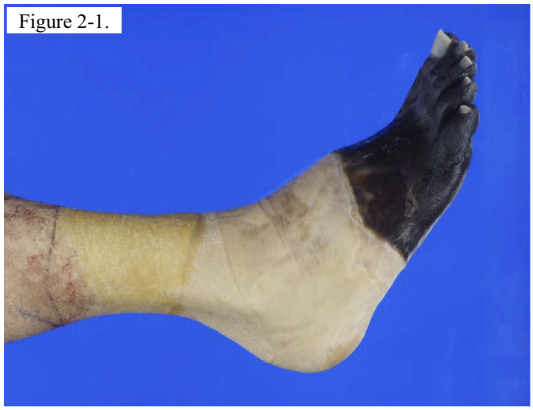
A physical examination showed a normal right popliteal pulse but reduced right dorsal pedis pulsation. Left popliteal, left dorsalis pedis, bilateral brachial, and radial pulsations were normal. A dermatological examination showed brown spots scattered over both lower legs, livedo reticularis on the right lower leg, and tender purpura scattered on the right foot and toes (Fig. 1A). The blood pressure was 136/66 mmHg. There was no claudication of the extremities or Raynaud's phenomenon. The lungs were clear on auscultation.

Laboratory findings were as follows: white blood cell count, 10,800/μL (neutrophils 90%, eosinophils 0.1%, and lymphocytes 6%); red blood cell count, 440×10^4/μL; hemoglobin, 11.8 g/dL; platelet count, 32.0×10^4/μL; activated partial thromboplastin time, 52.9 seconds (normal <36.3); D-dimer, 0.7 μg/mL; serum albumin, 4.1 g/dL; aspartate aminotransferase, 18 IU/L; alanine aminotransferase, 11 IU/L; urea nitrogen, 7 mg/dL; creatinine, 0.46 mg/dL; HbA1c, 6.3%; and C-reactive protein, 0.65 mg/dL. The levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were 79, 81, and 50 mg/dL, respectively. The serum IgG was 1,555 mg/dL, and complement components C3 and C4 were 99 and 11 mg/dL, respectively. Rheumatoid factor was negative, and anti-nuclear antibody was 1:160 with nucleolar and homogenous patterns. Anti-SS-A antibody was 1:4, and anti-SS-B antibody was negative. Results for myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) and serine proteinase3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) were negative. The lupus anticoagulant level was 2.35 (normal <1.3), and anti-cardiolipin IgM and IgG were 17 (normal <8) and 11.9 U/mL (normal <10), respectively. The results for anti-β_2 glycoprotein I antibody were negative. There was no evidence of cryoglobulinemia or cryofibrinogenemia. Urinalysis results were normal. Computed tomography angiography showed obstruction of the right anterior tibial artery and disruption of the right tibial artery and fibular artery. Skin biopsy specimens were obtained from the right plantar and the left foot, and those of the left foot demonstrated endothelial thickening and recanalization of small arteries.

The patient was initially considered as having PAN with anti-phospholipid antibodies. She was treated with methylprednisolone pulse therapy and intravenous cyclophosphamide pulse therapy, simultaneously with anticoagulants (heparin, followed by warfarin and thus achieving a target INR of 2.0) and antiplatelet agents (sarpogrelate hydrochloride or cilostazol), with no response. She was also administered vasodilators, such as bosentan and sildenafil with immunosuppressive therapies, which led to slight warming of her lower legs but no effect on the vasculopathy of the right foot and toes. Vasculopathy of the right foot and toes progressively worsened, and gangrene appeared (Fig. 1B, C). She developed severe foot pain, which was treated with opioids. Eighty days after admission, the patient underwent amputation of the right leg below knee.

Pathological findings of the amputated leg

Macroscopically, the right lower leg showed dry gangrene of the foot (Fig. 2-1). Microscopically, the anterior tibial artery, posterior tibial artery, and peroneal artery all showed



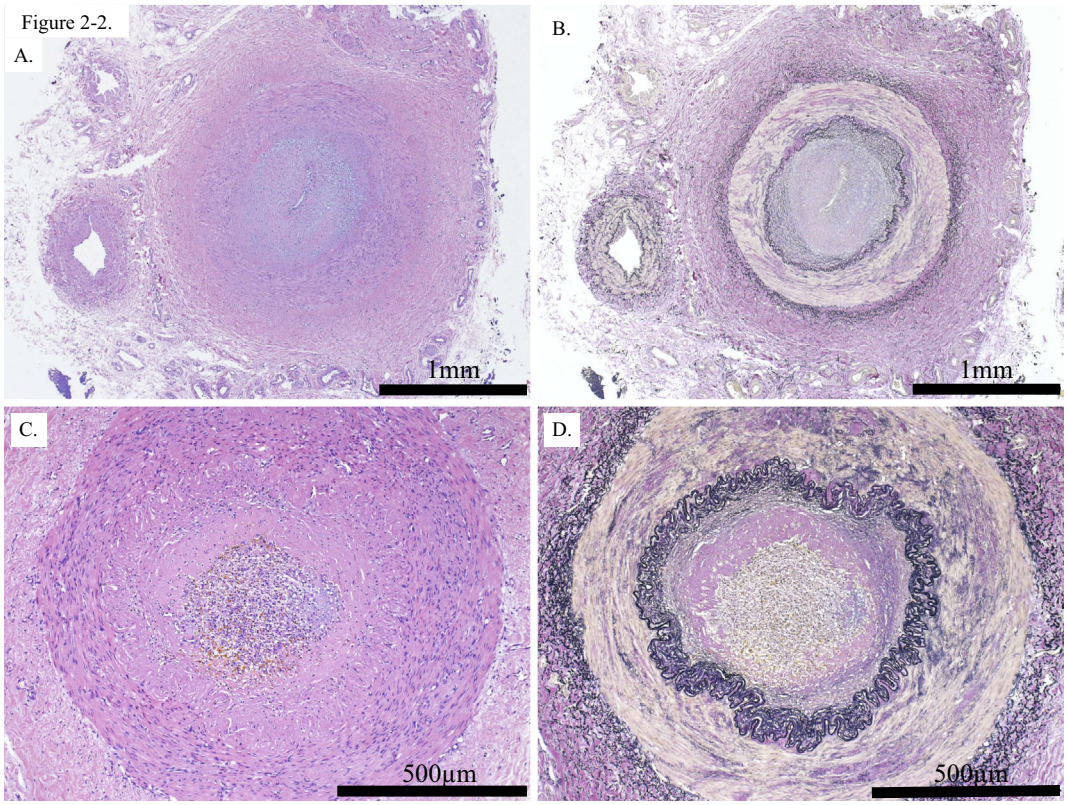


Figure 2. **(1) Macroscopic finding of the amputated right lower leg. Dry gangrene of the foot. (2) Microscopic findings. A: The anterior tibial artery (right) showed luminal occlusion with recanalization [Hematoxylin and Eosin (H&E) staining]. B: The internal elastic lamina of the artery was preserved, and fibrosis affected the adventitia and media (Elastica van Gieson staining). The accompanying vein (left) was essentially intact. C: The anterior tibial artery showed occlusion with organized thrombus. Lymphocytes had infiltrated the thrombus (H&E staining). D: The internal elastic lamina was preserved with newly formed multilaminate elastic lamina (Elastica van Gieson staining).**

luminal occlusion by organized thrombi with recanalization. Foci of lymphocytic infiltration in organized thrombi were observed. The internal elastic laminae were preserved with newly formed multilaminate elastic lamina. Fibrosis affected the adventitia and media. There was no fibrinoid necrosis, formation of granulomatous lesions, or evidence of atheromatous plaque and calcification. Accompanying veins were intact (Fig. 2-2). A few small arteries of the deep subcutaneous tissue showed organized thrombi. Neither necrotizing vasculitis nor leukocytoclastic vasculitis was observed in the small arteries of the dermis and subcutaneous tissues. The internal elastic laminae were normal. These findings were consistent with the subacute to chronic stage of TAO.

Discussion

Our patient was initially thought to have PAN with antiphospholipid antibodies due to the involvement of small- and medium-sized vasculitis and lupus anti-coagulant and anti-cardiolipin antibody positivity. However, the pathological findings of the amputated leg revealed TAO. If a pathological examination of the amputated leg had not been performed, the correct diagnosis might not have been made. She no longer requires glucocorticoids or immunosuppres-

sants.

Cases of non-smoking women with TAO with anti-phospholipid antibodies have rarely been reported. Until now, only two cases of female non-smokers from Turkey with TAO and anti-cardiolipin antibodies (aCL) have been reported. Case 1 was a 64-year-old woman diagnosed with TAO because of a history of several superficial thrombophlebitis attacks since 34 years of age. In that case, there was non-visualization of the right tibial artery and occlusion of the left distal posterior tibial and peroneal arteries and the right ulnar artery immediately before the palmar arch on arteriography. The patient had no atherosclerotic risk factors. Case 2 was a 34-year-old woman who had been evaluated for the first time for pain, paleness, hypothermia in her feet, and ulceration and dry gangrene of the right third toe. She had a history of three superficial thrombophlebitis attacks a year before her presentation. She was severely hypertensive and nondiabetic. Selective renal arteriography showed hemodynamically significant stenosis of bilateral renal artery origins. Arteriography showed patency of the iliac, femoral, and popliteal arteries. The tibial arterial systems were bilaterally filiform until their third distal segments. They had no clinical features of anti-phospholipid syndrome (APS) characterized by thrombocytopenia, recurrent abortion, or stroke (4).

The clinical association between aCL and TAO has been recognized. A retrospective study revealed that the prevalence of aCL was significantly higher in patients with TAO (36%) than in either those with premature arteriosclerosis (8%) or healthy individuals (2%). Patients with TAO and a high antibody titer tended to be younger and suffer a significantly higher rate of major amputation than those without the antibody (100% versus 17%). TAO and positivity for aCL may therefore be associated with a poor prognosis, including major limb amputation (7). Our patient was also positive for aCL, and her right lower leg had to be amputated. It is possible that her clinical course is consistent with that in previous reports. There are no prospective studies of TAO with aCL treated with anticoagulant or antiplatelet therapies because of its rarity.

There are few reports discussing vasculopathy of APS compared with TAO from a pathological standpoint. Vasculopathy in APS remains almost exclusively thrombotic in nature, although vasculitis may occasionally coexist in catastrophic APS; secondary APS associated with systemic lupus erythematosus; or, very rarely, capillaritis (8, 9). A dermatology review suggested that APS may result in occlusive non-vasculitic vasculopathy (10). A previous report suggested that pathological changes seen in anti-phospholipid arterial vasculopathy are quite different from those in TAO. Generally, infiltration of inflammatory cells is not present in patients with anti-phospholipid vasculopathy, in whom thrombosis appears in various stages of thrombus organization (11). In the present case, foci of lymphocytic infiltration in organized thrombi were observed, apart from gangrene, and the accompanying veins were intact. Therefore, a diagnosis of TAO was considered on the basis of the pathological findings, along with the absence of typical clinical features of APS, such as thrombocytopenia, recurrent abortion, stroke, or venous thromboembolism.

Although smoking is the most important risk factor of TAO, the essence of this relationship remains unclear at present (12). Endothelial cells may play a key role in the initiation and perpetuation of the inflammatory response. A cross-sectional study reported that TAO patients have an intrinsically reduced number of endothelial progenitor cells (EPCs), which have been identified as having reparative properties in the injured endothelium which are not entirely associated with smoking. This low number of EPCs may be responsible for the endothelial dysfunction seen in TAO patients, leading to the development of this disease at an early age. Low EPC numbers may cause endothelial dysfunction by impairing endothelial repair mechanisms and hampering neovascularization, which may contribute to the pathophysiology of TAO (13).

In conclusion, we encountered a case of a non-smoking woman with TAO who presented with severe pain and numbness of her right leg and foot that resembled PAN. Non-response to immunosuppressant and anti-coagulant therapies may be clues suggesting a reconsideration of the diagnosis. Regarding the clinical applicability of our findings in the management of similar cases in the future, we believe that our study will make a significant contribution to the literature.

The patient gave her written informed consent.

The authors state that they have no Conflict of Interest (COI).

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