

A Case of Azygos Vein Thrombosis Associated with Transient Antiphospholipid Syndrome in Urinary Tract Infection with *Escherichia coli*

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A 73-year-old female with diabetes admitted for treatment of an intertrochanter fracture of the femur and a urinary tract infection (UTI) with *Escherichia coli* developed thrombosis in her right azygos vein, which was thought to be associated with antiphospholipid and immunoglobulin M anticardiolipin antibodies. After antibiotic therapy, antiphospholipid antibody was undetectable, and a repeat chest computed tomography showed complete resolution of the azygos vein thrombosis. A wide variety of infections can be associated with thrombotic events in patients with transient antiphospholipid syndrome (APS), and this case serves as a reminder that the possibility of transient APS should be considered in patients with venous thrombosis in the setting of a UTI. (*J Rheum Dis* 2016;23:118-121)

Key Words. Antiphospholipid syndrome, Urinary tract infections, *Escherichia coli*

INTRODUCTION

The classical antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies (aPL)-that is, lupus anticoagulant or anticardiolipin antibodies- which bind target phospholipid molecules and are associated with recurrent fetal loss and thromboembolic phenomena [1]. Many infections may be accompanied by increases in aPL and, in some, these increases may be accompanied by clinical manifestations of APS [2]. Skin infections (18%), human immunodeficiency virus (HIV) infection (17%), pneumonia (14%), hepatitis C virus (13%), and urinary tract infections (UTI) are the most common “triggering” infections [2].

We report a case of thrombosis in the azygos vein associated with aPL immunoglobulin (Ig) M anticardiolipin antibody, in a 73-year-old woman. The patient was treated with antibiotics and the thrombosis resolved without

anticoagulant therapy.

CASE REPORT

A 73-year-old woman with type 2 diabetes mellitus was hospitalized with a fracture of the intertrochanter region of the femur and a UTI. The patient appeared severely ill. On admission, her body temperature was 36.8°C, pulse rate was 85 beats per minute, respiration rate was 20 times per minute and blood pressure was 140/95 mmHg. On initial physical examination, her oxygen saturation was 95% on room air and auscultation revealed equal air entry with normal breath sound and regular heart sounds. Laboratory tests showed a white blood cell count of 10,340/ μ L with 79.5% segmented neutrophils, a hemoglobin of 10.1 g/dL, platelets of 140,000/ μ L, erythrocyte sedimentation rate of 106 mm/h, and a C-reactive protein of 7.989 mg/dL. Her plasma glucose was 345 mg/dL and

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hemoglobin A1C was 11.8%. She was HIV and venereal disease research laboratory negative. Chest X-ray showed no active lesions in the lung. Urinalysis showed 4+ albumin and too numerous to count white blood cells and red blood cells. We decided that it would be best for the patient to control blood glucose levels and treat her UTI before surgery for the intertrochanteric fracture. She was started on insulin and initial empiric antibiotic therapy was ciprofloxacin 400 mg intravenously every twelve hours for a presumed UTI. On day 5 of the admission, the patient's urine cultures yielded ciprofloxacin-resistant *Escherichia coli*. Ciprofloxacin was discontinued on day 3 of the admission and meropenem at 1,000 mg intravenously every eight hours was begun. On the same day, the patient developed sudden shortness of breath and bilateral lower extremity swelling. Chest X-ray revealed pulmonary edema and effusion. Further imaging with contrast enhanced helical computed tomography (CT) showed a filling defect noted in the azygos vein consistent with venous thrombosis without pulmonary emboli (Figure 1). Transthoracic echocardiography revealed normal left ventricular function with no vegetation, valvular regurgitation, and other signs of endocarditis. Lower extremity Doppler ultrasound did not show deep vein thrombosis. The patient's antinuclear antibody was weakly positive with a nucleolar type. However, there was no hypocomplementemia or ds-DNA antibody. A lupus anticoagulant, anti-beta 2 glycoprotein I (β_2 GPI) antibody, IgG, IgM anti-phospholipid antibody, and IgG anticardiolipin antibody (aCL) were normal, but IgM aCL was moderately elevated to 100 IgM phospholipid unit (MPL) (<20 MPL). Coagulation tests revealed a normal prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrin degradation products (FDP) but a

marked elevation of D-dimer levels ($46.8 \mu\text{g/mL}$). There were normal serum protein C and P levels; 1.15 and 0.64 U/mL (0.65 to 1.35 U/mL and >0.63 U/mL, respectively). We postponed the use of anticoagulants after intertrochanteric fracture surgery and performed conservative management with oxygen supply and diuretics. After 7 days of antibiotic therapy, the patient's clinical condition had improved and subsequent chest X-ray showed gradual resolution of pulmonary edema and pleural effusion. In addition, the presence of serum aPL spontaneously disappeared and a repeat chest CT revealed complete resolution of the thrombotic obstruction in the right azygos vein without anticoagulant therapy after 12 weeks (Figure 2).

DISCUSSION

In this case, pulmonary embolism was suspected since the patient had a Wells criteria score of 3 [3], and although a score of 3 carries low probability, contrast enhanced helical CT of the chest showed thrombotic occlusion of the azygos vein. This patient had many coagulation risk factors including old age, fracture, and immobilization. We excluded other coagulation disorders by laboratory tests such as anti-thrombin III, FDP, and platelet count. Causes of coagulopathy such as protein C and S deficiency were not thought to play a role in azygos vein thrombosis because of the normal results on laboratory testing. However, the patient had a moderately elevated IgM anticardiolipin antibody detected in serum using enzyme-linked immunosorbent assays. According to the revised Sydney criteria in 2006, APS is present in patients with 1 clinical and 1 laboratory criterion [4]. Laboratory criteria include medium or high titer IgG or



Figure 1. Contrast enhanced chest computed scan, axial image at pulmonary trunk bifurcation and coronal reformation, showed filling defects in the azygos vein (arrows).



Figure 2. Follow-up of chest computed tomography revealed complete resolution of the embolism in the azygos vein (arrows).

IgM aCL or the presence of lupus anticoagulant on 2 or more occasions at least 12 weeks apart [4]. In this case, the patient also showed 1 clinical, azygos vein thrombosis and 1 laboratory criteria, serum IgM aCL, although aCL disappeared after 12 weeks. aPLs are a heterogeneous group of autoantibodies or alloantibodies with an affinity for anionic phospholipids [5]. In the general population, 1% to 5% of people have positive aPL [6]. Infection-associated aPL appear temporarily and disappear within 2 or 3 months in most cases. Usually, they do not cause thrombotic complications [7]. Therefore, transient aPL must be interpreted carefully. In our case, IgM aCL resolved after 12 weeks and appropriate antibiotic therapy. We considered that this transient aPL to be associated with infection, but also considered the possibility of transient APS.

APS associated with various infections can incite thrombotic events [2]. Many bacterial infections demonstrate aPL, although a pathogenic role for these antibodies has not usually been observed, except in a few isolated cases [8]. *E. coli* is known as one a pathogen related to APS (4%) [2]. The pathogenesis of *E. coli* related APS is not known. *E. coli* can produce heterologous proteins such as human β_2 GPI thought to contain crucial antibody binding epitopes for aPL, which can be critical in the pathogenesis of APS [9]. In our case, the antiphospholipid antibody spontaneously disappeared and a repeat chest CT revealed complete resolution of thrombotic obstruction in right azygos vein without anticoagulant therapy and after the infection had resolved. There have been two reports that point to the effectiveness of antibiotics in APS. In a patient with APS associated with *Helicobacter pylori*, all disease manifestations disappeared upon eradication of the bacteria [10]. In an experimental model of APS, the mani-

festations were relieved with parallel treatment with ciprofloxacin [11].

Anticoagulant therapy with prompt antibiotic coverage has been suggested for the treatment of transient APS [2]. Although anticoagulation is the cornerstone of treatment for deep venous thrombosis, antibiotics have been used without anticoagulants in our patient because there was no thrombosis in the pulmonary vein or venae cavae. Embolism can theoretically affect any vein in the body, both superficial and deep. However, embolism in the azygos vein is extremely rare [12,13]. The azygos vein connects the superior vena cava and inferior vena cava and can provide an alternative path for blood to the right atrium when either of the venae cavae is obstructed [14]. As a result, azygos vein obstruction theoretically may have no clinical meaning if there was patency of both venae cavae; it is usually asymptomatic if it is not accompanied by obstruction of the pulmonary vein or venae cavae [12,15]. In addition, surgery for intertrochanter fracture was planned for the next day. Antithrombotic agents would be contraindicated if the thrombosis was due to septic emboli. It may be difficult to adequately manage septic patients with venous thrombosis because of high risk for complications such as worsening sepsis, metastatic infection, and pulmonary embolism. Early administration of intravenous heparin followed by oral anticoagulant therapy in patients with septic embolism remains controversial [12].

SUMMARY

In summary, we should consider the possibility of transient APS in patients with venous thrombosis in the setting of a UTI. Use of anticoagulants must be carefully con-

sidered in infection induced transient APS accompanied with azygos vein thrombosis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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