Antiphospholipid Syndrome: A Paraneoplastic Phenomenon Unmasking Occult Extragonadal Seminoma

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Antiphospholipid syndrome (APS) is a disorder defined by recurrent vascular thrombosis, pregnancy loss, or thrombocytopenia and the presence of persistently elevated levels of antiphospholipid antibodies. This syndrome develops secondary to systemic lupus erythematosus and other autoimmune disorders, infections, use of certain drugs, and malignancy. Primary APS occurs in isolation and is idiopathic. This article describes the case of a patient with recurrent deep venous thrombosis (DVT) caused by APS that presented as a paraneoplastic phenomenon, unmasking an occult retroperitoneal seminoma.

CASE PRESENTATION

Initial Presentation and Evaluation

A 46-year-old man presented to the emergency department complaining of swelling and pain affecting his right lower extremity that was found to be caused by DVT as shown by Doppler ultrasonography. His past medical history was significant for an undescended right testicle that was surgically corrected by inguinal orchiopexy at age 6 years as well as a superficial lower extremity thrombophlebitis that had been diagnosed several months prior. Initial laboratory studies revealed an elevated partial thromboplastin time (PTT) of 43.6 sec (normal, 22–34 sec), a prothrombin time (PT) of 11.8 sec (normal, 11–13 sec), and an international normalized ratio (INR) of 1.05. Review of the patient's medical records showed that his PTT 6 months ago was 81.6 sec, PT was 15.3 sec, and INR was 1.79. In addition, complete blood count at the current presentation showed thrombocytopenia of 93,000 cells/μL (lower normal limit, 150,000 cells/μL). The patient's IgG anticardiolipin level was greater than 80 GPL units (high positive), while the test for IgM anticardiolipin antibodies was negative. These findings were highly suggestive of APS. The remainder of the hypercoagulability tests were unremarkable.

Further Work-up

Secondary causes of APS were sought, including malignancy and rheumatic disorders. Computed tomography (CT) of the chest was negative, while abdominal CT showed a 3 × 2 cm retroperitoneal lymph node anterior to the inferior vena cava (**Figure 1**). Because of the location of the enlarged lymph node and given the history of an undescended testicle, the possibility of a gonadal neoplasm was considered. Testing revealed a mildly elevated level of α-fetoprotein at 10.9 ng/mL (normal, 0.0–8.8 ng/mL), while a β-human chorionic gonadotropin assay was negative. Ultrasonography of the testicles showed an atrophic right testicle with a heterogeneous density suspicious for malignancy. Subsequently, the patient underwent orchiectomy that revealed an atrophic testicle with no evidence of neoplastic changes.

The etiology of the enlarged retroperitoneal lymph node was still unclear. CT-guided biopsy of the lymph node was deferred due to the close proximity to the inferior vena cava, and thus an open laparotomy was performed. Histopathologic evaluation of the resected lymph node revealed features consistent with an extragonadal seminoma (**Figure 2**). The patient was further treated with radiotherapy, to which he had an excellent response. He was placed on warfarin during the 12 months of treatment. Four-years after being diagnosed and treated, the patient has had no recurrence of the seminoma or thrombosis and does not require anticoagulation therapy.

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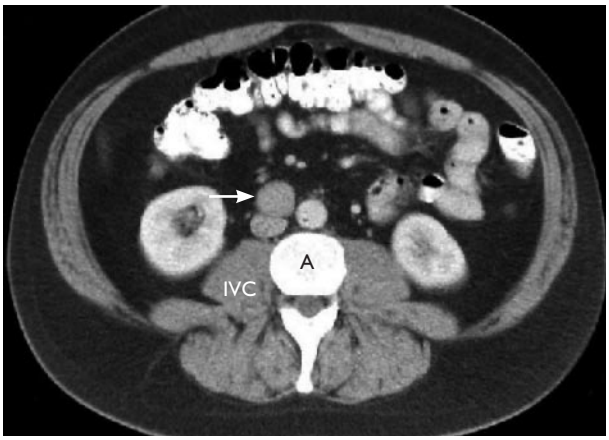

Figure 1. Abdominal computed tomography scan showing an enlarged retroperitoneal lymph node (*arrow*) compressing the inferior vena cava (IVC) anterolateral to the abdominal aorta (A).

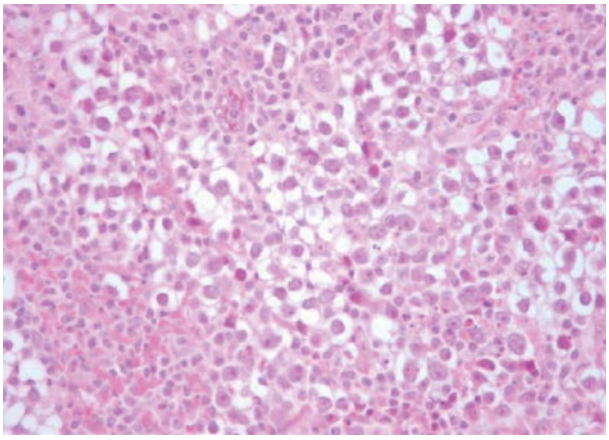

Figure 2. Open biopsy of the enlarged retroperitoneal lymph node revealed the diagnosis of seminoma. It is characterized by large cells with clear cytoplasm aggregated in nests separated by thin septa of infiltrating lymphocytes.

HYPERCOAGULABILITY IN MALIGNANCY

The association between hypercoagulability and cancer was first noted by Trousseau in 1865.[1] Since then, the term *Trousseau's syndrome* has been used in reference to recurrent episodes of migratory venous and/or arterial thrombosis occurring in patients with underlying malignancy.[2] Further studies have shown that DVT and pulmonary embolism occur in 10% to 50% of patients with cancer.[3] Thrombosis has been associated with all kinds of cancers and is triggered by tissue factor, cancer procoagulant, and/or various cytokines.[4,5] The term *Trousseau's syndrome* is used broadly to refer to any form of hypercoagulability associated with cancer regardless of the etiopathologic mechanism. APS as a paraneoplastic phenomenon represents an autoimmune-mediated form of Trousseau's syndrome.[6] Cancer-related APS has been associated with a variety of malignancies, including solid tumors and hematologic neoplasms. Besides malignancy, secondary forms of APS occur with infections, connective tissue disorders, and use of certain drugs, while the primary form of this disease is idiopathic.[7,8]

Approximately 20% of patients presenting with DVT have a known active malignancy. In addition, studies have shown that an occult malignancy is identified at the time of the idiopathic thrombotic event in more than 3% of patients, and this number increases to 10% after 6 months.[7,9,10] Moreover, the Montpelier Antiphospholipid Study has shown that 19% of patients with APS have a known or occult malignancy.[10] It is important to keep in mind that thrombotic events associated with antiphospholipid antibodies can be the first manifestation of an occult malignancy.[11]

APS is characterized by the presence of antibodies (anticardiolipin antibodies, anti-β2-glycoprotein I, and lupus anticoagulant) directed against either phospholipids or plasma proteins bound to anionic phospholipids. Clinically, the syndrome manifests as recurrent fetal losses, noninfectious endocarditis, thrombocytopenia, incidental prolongation of a test of blood coagulation (eg, PT or PTT), or, most commonly, venous or arterial thrombosis.[9,12,13]

For patients with cancer-related thrombophilia, therapy should target the underlying malignancy. Because the patient will continue to be at high risk for recurrent thrombotic events as long as the tumor persists,[14] anticoagulation serves as a method of prophylaxis and treatment. Anticoagulation may be achieved with unfractionated heparin, low molecular weight heparin (LMWH), or warfarin. Many patients with Trousseau's syndrome have a poor response to warfarin.[14] Recent studies have demonstrated that LMWH provides better control of the thrombosis and hypercoagulability associated with malignancy compared with unfractionated heparin.[14,15]

Extragonadal Germ Cell Tumors

The origin of primary extragonadal germ cell tumors (EGGCTs) is unclear. Most likely they arise outside the gonads, although there are studies indicating evidence of burnt-out gonadal malignancy in many cases of EGGCT.[16] These cancers are uncommon and represent less than 4% of all germ cell tumors. Typically, EGGCTs arise in midline locations, with the most common sites being the anterior mediastinum, retroperitoneum, and pineal and suprasellar regions. EGGCTs are histologically

classified as teratomas or nonteratomas. The latter include seminomas and malignant nonseminomas. EGGCTs are usually diagnosed in advanced stages, as they remain asymptomatic for long periods of time.[17,18]

CONCLUSION

The case presented in this article is, to the best of our knowledge, the first reported case of APS as the initial presentation of extragonadal seminoma. The work-up of APS in this case led to early diagnosis of a malignancy at a potentially curable stage. This example serves as a reminder that the differential diagnosis of secondary APS includes occult malignancy and that diagnosis at an early stage can result in a considerably improved prognosis. **HP**

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