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A Case of Antiphospholipid Syndrome Following Gastric Signet Ring Cell Adenocarcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 53-year-old
Final Diagnosis: —
Symptoms: Antiphospholipid syndrome (APS)
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease

Background: Antiphospholipid syndrome (APS) is a rare autoimmune disease characterized by arterial, venous, and small-vessel thrombosis, pregnancy-related morbidity and the presence of antiphospholipid antibodies such as anticardiolipin antibody, and/or anti-beta2-glycoprotein I. In the recent years, APS was observed in patients with solid tumors and the renal cancer, lung carcinoma and breast tumors were the most common tumors linked with APS.

Case Report: A 53-year-old female presented with pain and pitting edema of left lower extremity that had begun 6 months prior to hospitalization. Deep vein thrombosis (DVT) in the popliteal vein diagnosed by Doppler ultrasonography and the patient was treated with heparin followed by warfarin. Following subdural hematoma, anticoagulant therapy was stopped, and the patient underwent craniotomy. One month later, the patient returned with pain and DVT diagnosed in its right leg. Laboratory tests showed high levels of lupus anticoagulant, IgM and IgG anticardiolipin antibodies. Following a high alkaline phosphatase, diffuse bone marrow involvement was found by whole body bone scan. Looking to find primary tumor, a large infilterable lesion in gastric was seen by endoscopic images, and biopsy histopathology showed a signet ring cell adenocarcinoma. The patient refused chemotherapy and died 6 months after diagnosis.

Conclusions: APS is associated with gastric signet ring cell adenocarcinoma.

MeSH Keywords: Antibodies, Anticardiolipin • Antiphospholipid Syndrome • Stomach Neoplasms

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Background

Antiphospholipid syndrome (APS) is a rare autoimmune disease characterized by arterial, venous, and small-vessel thrombosis, pregnancy-related morbidity and the presence of antiphospholipid antibodies such as anticardiolipin antibody, lupus anticoagulant, and/or anti-beta2-glycoprotein I [1]. There are several reports on the association between APS and malignancies [2]. The presence of APS in patients with solid tumor is linked with thrombotic complications. The review of cases with APS and tumor revealed that the renal cancer, lung carcinoma and breast tumors were the most common tumors linked with APS. Only 1 case of stomach cancer with APS was found in the literature [3]. Here, we report a case of APS following gastric signet ring cell adenocarcinoma.

Case Report

A 53-year-old female was referred to our hospital with pain and pitting edema of left lower extremity that had begun 6 months prior to hospitalization. Deep vein thrombosis (DVT) in the popliteal vein diagnosed by color Doppler ultrasonography. The patient treated with 1100 U/hour heparin and discharged from the hospital on warfarin 5 mg daily with international normalized ratio (INR) 2.2 after pain relief. The patient returned 1 month later, and a cerebral computed tomography (CT) scan revealed a subdural hematoma in hemisphere. This hematoma caused mass effect to lateral ventricle and subfalcine herniation. Following subdural hematoma, anticoagulant therapy was stopped, and the patient underwent craniotomy. One month after the craniotomy, the patient returned with pain and swelling of right leg. She had anorexia and weight loss of 4 kg over the last 4 months. On examination, body temperature, blood pressure, pulse rate, and respiratory rate were 36.5°C, 120/80 mm Hg, 78 beats, and 14 breaths per minute, respectively. Heart and lung auscultation were normal. The patient had mild epigastric tenderness without rebound. Difference between distal and proximal of right and left lower extremity was about 4 cm. Color Doppler ultrasonography showed DVT in the popliteal vein. Inferior vena cava (IVC) filter placed in the patient because of the history of intra-cranial bleeding. Follow-up laboratory tests showed a thrombocytopenia and a prolonged partial thromboplastin time (PTT) despite stopping the anticoagulants. Hemoglobin concentration was reduced to 8.6 g/dL (normal: 11.3–14.5 g/dL) and platelet count was 47 000/µL that was below normal range (150 000–450 000/µL). The C-reactive protein was 51 mg/dL (normal <0.2 mg/dL) and erythrocyte sedimentation rate (ESR) was 114 mm/hour (normal <15 mm/hour). C3 (90–180 mg/dL), C4 (13–75 mg/dL), and total complement activity (CH50) were in normal level. APS was suspected so serology was sent and it showed a high titer (45 U/mL) of IgM anticardiolipin antibodies

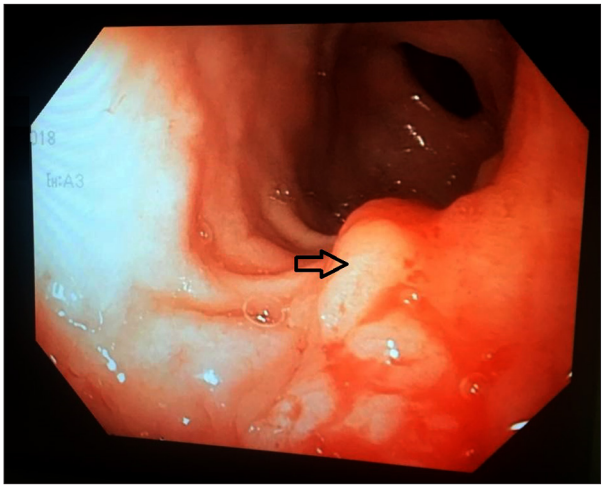

Figure 1. Upper gastrointestinal endoscopy showing a large infilterable lesion (4×3 cm) located in the body of stomach (arrow). The surrounding mucosa was not combined with atrophy or intestinal metaplasia.

(normal <18 U/mL), IgG anticardiolipin antibodies equal to 55 U/mL (normal <18 U/mL), and lupus anticoagulant equal to 48 U/mL (normal <35 U/mL). Anti-double stranded DNA (anti-dsDNA), and antinuclear antibody (ANA) were negative. Alkaline phosphatase (ALP) was increased to 3783 U/L (normal: 20–70 U/L), and the level of gamma glutamyl transferase (GGT) was 35 U/L (6–37 U/L). Therefore, the whole-body bone scan was performed to detect infiltrative bone disease in the patient suspected to APS. The scan showed nonhomogeneous radiotracer uptake in the skull, spine, pelvic, and faint foci of increased radiotracer uptake in the proximal portion of both femurs. This result suggested bone metastasis. Upper endoscopy was performed as a part of work up for the primary tumor, which revealed a large infilterable lesion (4×3 cm) in the stomach (Figure 1). A biopsy was taken which showed adenocarcinoma with signet ring cell component. Histologic analysis of the gastric biopsy shows atypical cells with hyperchromatic nuclei and eosinophilic cytoplasm are arranged as glandular structures. (Figure 2). Other organs were checked for metastasis. Triphasic CT scan of the abdomen showed hypodense lesions in the liver resembling metastases. In chest CT scan, small nodules seen in right lung and metastatic lesions in the vertebra. Thyroid sonography revealed multiple calcified nodules in both lobes. The patient refused chemotherapy and died 6 months after diagnosis.

Discussion

The APS is diagnosed when the patient has least one clinical and one laboratory criterion. Vascular thrombosis and pregnancy morbidity are clinical criteria. Lupus anticoagulant, anticardiolipin-antibodies (with titer >99th percentile), anti-β2

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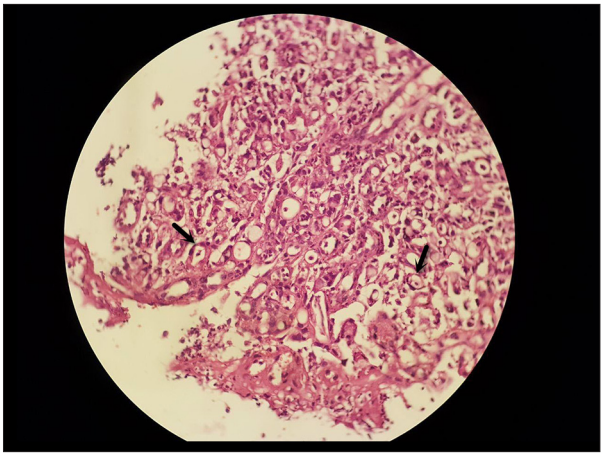

Figure 2. Histologic analysis of the gastric biopsy shows signet ring cell carcinoma. Atypical cells with hyperchromatic nuclei and eosinophilic cytoplasm are arranged as glandular structures. Some neoplastic cells have lateral nucleus and cytoplasmic mucin vacuoles matched with ring cells (arrows) that invaded the lamina propria.

glycoprotein-I-antibodies (with titer >99th percentile) that is confirmed by repeat testing with an interval of at least 12 weeks are laboratory criteria. In the present case, the patient had an ultrasound confirmed DVT and high titer of IgM/IgG anticardiolipin and lupus anticoagulant. The presence of lupus anticoagulant is a strong risk factor for venous thrombosis in APS, while the association between levels of anticardiolipin-antibodies antibodies and thrombosis is less clear. Several studies have reported that the risk of venous thrombosis increases with the number of positive tests for antiphospholipid antibodies. APS can be associated with the non-criteria manifestations, such as heart valve disease, livedo reticularis, thrombocytopenia, superficial vein thrombosis, renal microangiopathy, seizures, chorea, myelitis, and systemic lupus erythematosus (SLE)-like symptoms (e.g., alopecia, aphthous ulcers). In this case, the patient had thrombocytopenia (PLT <50 000) as a non-criterion clinical manifestation of APS.

Previous studies have shown that antiphospholipid antibodies can be associated with malignancies [2]. In this case, titer of lupus anticoagulant, IgM and IgG anticardiolipin antibodies were moderate to high in a patient with DVT and gastric cancer. Ozguroglue et al. showed an association between high level of anticardiolipin antibody and thromboembolic events in patients with colorectal, breast, ovarian, lung, and pancreatic cancer [4].

The literature review of cases with APS and solid tumors showed that kidney cancer, tumors with unknown origin, lung adenocarcinoma, and breast cancer were the common tumors related with antiphospholipid antibodies [1]. Only 1 case of stomach cancer linked with APS was found among the published articles [3]. They were detected anticardiolipin and anti-beta-2 glycoprotein I antibodies in the serum of a 45-year-old female with gastric cancer. Their case had only hypertension in her medical history without other illnesses, miscarriages, or thrombotic events. A history of SLE was in her family and her daughter had died with SLE, but in the present case, the patient did not have a family history of SLE. The first finding in their case was lesions resembling metastases in the liver, spleen, and kidney, then antiphospholipid antibodies detected in serum, whereas we first detected APS and then found the cancer. Despite the findings in this case and previous data on the possible pathogenic role of antiphospholipid antibodies, proving a direct association between APS and the cancer is difficult. However, the clinical findings described in our present case and the positivity of antiphospholipid antibodies suggested an association between the 2 disorders.

Thrombosis is one of the first manifestations of malignancy. Cancer patients are at high risk of thromboembolic events [5]. The association between antiphospholipid antibodies and thrombotic events was found since the 1980s [6]. During the last decades, several case reports of APS in patients with thrombosis and various types of cancer such as non-Hodgkin lymphoma, breast, colorectal, ovarian, and lung carcinoma have been published [7]. Therefore, antiphospholipid antibodies may be linked to tumor-related thrombosis. These antibodies may be increased due to cancer immunotherapy by interferon α or immune response to tumor antigens [2]. Cancers can increase the production of antiphospholipid antibodies by several mechanisms including the following: 1) autoantibody production in response to tumor antigens; 2) secretion of anticardiolipin antibodies from tumor cells; and 3) production of monoclonal immunoglobulins with lupus anticoagulant and anticardiolipin-antibodies activities.

In the present case, heparin was first used for treatment of DVT followed by warfarin. Anticoagulation therapy was stopped following subdural hematoma. Low molecular weight heparin and subsequent vitamin K antagonists are first-line treatments for venous thrombotic event. The use of direct oral anticoagulants for treatment is not recommended. After low molecular weight heparin therapy in the acute phase, treatment can be switched to vitamin K antagonists (INR target range of 2.0–3.0). Treatment with an INR more than 3.0 after a first venous thrombosis is not recommended.

Unfortunately, the patient reported in this study refused chemotherapy and died 6 months after diagnosis. In several previous reports, patients underwent chemotherapy or checkpoint inhibitor therapy, and survived. In recent years, immune checkpoint inhibitors (ICIs) have been recommended for treatment of advanced cancers. Anti-PD-1/PD-L1 antibodies have shown an acceptable clinical activity in gastric cancer and can be a new treatment option [8,9].

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Conclusions

In this present case, we found an APS associated with gastric signet ring cell adenocarcinoma. Despite the findings in this case and previous data on APS and cancer, proving a direct association between APS and the cancer was difficult. However, the clinical findings described in the present case and the positivity of antiphospholipid antibodies suggested an association between the 2 disorders.

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Conflicts of interest

None.

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