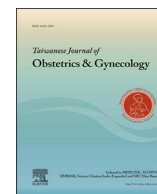




Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Systemic embolic events with nonbacterial thrombotic endocarditis as manifestations of recurrent ovarian clear cell carcinoma



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ARTICLE INFO

Article history:

Accepted 11 August 2014

Keywords:

noninfective endocarditis
ovarian neoplasms
recurrence
stroke

ABSTRACT

Objective: To present a rare case of recurrent ovarian clear cell carcinoma (OCCC) with systemic embolic events.

Case report: A 60-year-old woman with a history of OCCC presented with an acute ischemic stroke. Magnetic resonance imaging showed multifocal, bilateral infarctions over the cerebrum and cerebellum. An echocardiogram revealed vegetation growth in the mitral and tricuspid valves and showed no evidence of atrial fibrillation. The serological studies for stroke were negative for all assessed parameters (normal values of protein C, protein S, antithrombin III, and lupus anticoagulant antibodies). Computed tomography of the abdomen and pelvis revealed bilateral renal and splenic infarctions, as well as enlarged pelvic lymph nodes due to a recurrent ovarian neoplasm. We diagnosed the patient with nonbacterial thrombotic endocarditis (NBTE) based on serial negative blood cultures and sterile vegetation of the surgical specimen.

Conclusion: NBTE should be considered among the possible causes of multifocal embolic infarctions and as an early manifestation of recurrent OCCC. Anticoagulant therapy is the mainstay of treatment, and dual anticoagulation therapies are necessary to reduce the risk of recurrent thromboembolism.

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Introduction

Women with ovarian cancer may present with a range of symptoms, including bloating, pelvic or abdominal pain, difficulty eating, early satiety, urinary urgency, or increased frequency of urination [1]. Nonbacterial thrombotic endocarditis (NBTE), also known as marantic endocarditis, is a rare manifestation in ovarian cancer and usually precedes the diagnosis of malignancy [2]. NBTE is characterized by deposition of fibrin and platelets on the heart valves in the absence of a bloodstream bacterial infection and acute inflammatory reaction, which predominantly occurs in mucin-

producing adenocarcinomas, such as acute leukemia or pancreatic, lung, and gastric cancers [3,4].

In this paper, we describe a rare case of recurrent ovarian clear cell carcinoma (OCCC) in a 60-year-old woman who developed aseptic vegetation on the mitral and tricuspid valves and experienced systemic embolisms.

Case Report

A 60-year-old woman presented with acute onset of an unstable gait, urinary incontinence, apathy, and mutism for 3 days. The patient's medical history included Type 2 diabetes mellitus, hypertension, and Stage IIIC OCCC, which was treated with debulking surgery followed by five cycles of adjuvant chemotherapy 10 years previously. Postoperatively, the patient had regular follow-up visits for 5 years at the Gynecological Outpatient Department (Tri-Service General Hospital, Taipei City). The patient denied any symptoms of bloating, abdominal pain, or early satiety. Regular computed

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tomography (CT) revealed no evidence of para-aortic lymph node enlargement or ascites (Figure 1A), and her cancer antigen-125 (CA-125) level was 14.29 U/mL (normal range 0–35 U/mL). Her family history indicated that one brother developed lymphoma, and another was diagnosed with hepatocellular carcinoma. On initial physical examination, she was in no acute distress, was afebrile, and had a heart rate of 80 beats/min with normal blood pressure.

Cardiac examination revealed a normal rhythm with no detectable murmurs or irregular sounds, and her lungs were clear on auscultation. An abdominal examination by palpation demonstrated no tenderness or a palpable mass. A neurological examination revealed acalculia, mutism, and recent memory impairment. Initial laboratory study results were as follows: white blood cell count of $6.66 \times 10^3/\mu\text{L}$ with a neutrophil count of $4.51 \times 10^3/\mu\text{L}$; hemoglobin level of 10.1 g/dL; platelet count of $124 \times 10^3/\mu\text{L}$; troponin level of 0.45 ng/mL; total creatine kinase level of 154 U/L; creatinine level of 0.9 mg/dL; international normalized ratio of 1.1; prothrombin time of 11.9 seconds; partial thromboplastin time of 24.9 seconds; fibrinogen level of 627.9 mg/dL; fibrin degradation products of 8301 ng/mL; and D-dimer level of 11.94 mg/L. Her electrocardiogram monitoring showed findings consistent with a normal sinus rhythm.

A stroke protocol was initiated, and magnetic resonance imaging of the brain showed diffuse acute lacunar infarcts in the bilateral cerebra and cerebella without occlusion or stenosis of the intracranial arteries (Figure 2), suggestive of an embolic stroke. An echocardiogram showed severe mitral regurgitation and oscillation, with moderate-sized vegetation on the mitral valve leaflet ($0.7 \times 0.6 \text{ cm}^2$; Figure 3A) and tricuspid valve leaflet ($0.6 \times 0.5 \text{ cm}^2$; Figure 3B). Other confounding factors for stroke, including levels of protein C, protein S, immunoglobulin, antithrombin III, anticardiolipin immunoglobulin G, lupus anticoagulant, antistreptolysin O titer, rheumatoid factor, rapid plasma reagin, and antihuman immunodeficiency virus antibodies, were within normal limits. Tumor markers were assessed, and the level of CA-125 was 133.9 U/mL (normal range 0–35 U/mL). The patient was lost to follow up at the Gynecological Outpatient Department for approximately 5 years. Based on the neuroimaging results, cancer-related hypercoagulation resulting in acute ischemic stroke was still strongly considered at the time of the stroke attack. Therefore, tumor markers were evaluated accordingly, and the level of CA-125 was found to be 133.9 U/mL (normal range 0–35 U/mL). The gynecology specialist was consulted regarding the elevated CA-125 level. Pelvic examination and transvaginal ultrasound showed absence of the uterus and ovaries, however, mild ascites was observed over the pelvis. Recurrent OCCC was suspected.

A CT examination was performed for recurrent malignancy work-up and showed numerous large, edge-shaped hypodensities in the spleen and bilateral kidneys (Figure 1B), consistent with infarcts. Enlarged nodes (size $< 2.7 \text{ cm}$) were noted in the para-aortic space, and in the right common and internal iliac chains (Figure 1C), indicating recurrent OCCC. The patient did not undergo tissue biopsy due to coagulopathy and the deep location of the tumor and nodes.

The patient was suspected of having infective endocarditis, and empiric therapy was initiated with ceftriaxone plus vancomycin. Despite persistent low-grade fevers, serial blood cultures remained sterile. The patient received an antiplatelet agent (ticlopidine 250 mg/d) and anticoagulation therapy with a vitamin K antagonist (warfarin 2 mg/d) for secondary stroke prevention. However, a stroke-in-evolution was noted, with new onset of motor aphasia and right-sided hemiparesis during hospitalization. Heparin infusion was initiated immediately, and the patient's neurological deficits improved partially. On Day 14 of hospitalization, the patient underwent surgery for removal of the vegetations and valve replacement to prevent recurrent embolic events. The sterile nature of the vegetations was confirmed by pathological examination and negative cultures of the surgical samples. A diagnosis of infective endocarditis was therefore excluded. The patient was successfully extubated on postoperative Day 4 and transferred to a standard hospital room. A gynecology specialist was consulted, and chemotherapy was suggested for control of the underlying malignancy. Dual anticoagulation therapies of oral warfarin and intravenous heparin were initially administered after the surgery. Unfortunately, the patient died of pneumonia with sepsis on hospital Day 29.

Discussion

Patients with cancer are in a hypercoagulable state. Thrombotic events may precede the diagnosis of malignancy in migratory superficial thrombophlebitis (Trousseau's syndrome), chronic disseminated intravascular coagulation, or NBTE [2]. Adenocarcinoma of the ovary has been previously described as a cause of NBTE, however, only three cases of OCCC have been reported in the literature [5–7].

Our case presentation is the first to describe the relationship between tumor recurrence and NBTE. Our patient initially presented with recurrent OCCC along with acute multifocal cerebral and cerebellar infarctions. A transthoracic echocardiogram identified severe mitral regurgitation and oscillating, moderate-sized vegetation on the mitral valve leaflet and tricuspid valve leaflet. A contrast-enhanced CT scan of the abdomen showed numerous

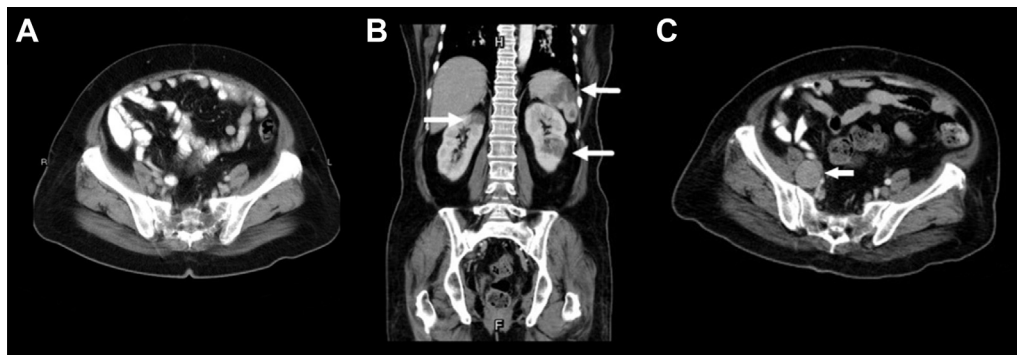


Figure 1. Contrast-enhanced computed tomography revealed (A) no evidence of para-aortic lymph node enlargement or ascites, but did show (B) multiple low-density lesions in the spleen and kidneys and (C) enlarged nodes (size $< 2.7 \text{ cm}$) in the right pelvic cavity, findings consistent with recurrent tumor with embolic infarcts. The ovary and uterus were removed.

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