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Case Report

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

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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.

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/μL with a neutrophil count of 4.51 $\times$ 10^3/μL; hemoglobin level of 10.1 g/dL; platelet count of 124 $\times$ 10^3/μL; 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 cm^2; Figure 3A) and tricuspid valve leaflet (0.6 $\times$ 0.5 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 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

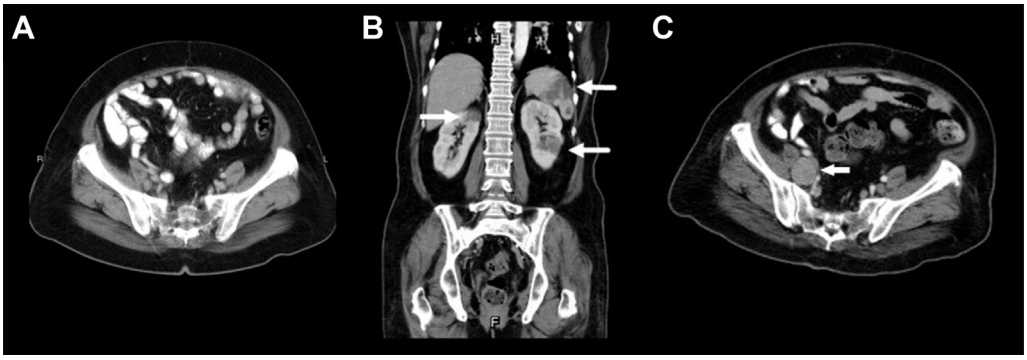

Figure 1. Contrast-enhanced computed tomography revealed (A) no evidence of para-aortic lymph node enlargement or ascites, but did show (B) multiple low-density lesions in the spleen and kidneys and (C) enlarged nodes (size < 2.7 cm) in the right pelvic cavity, findings consistent with recurrent tumor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

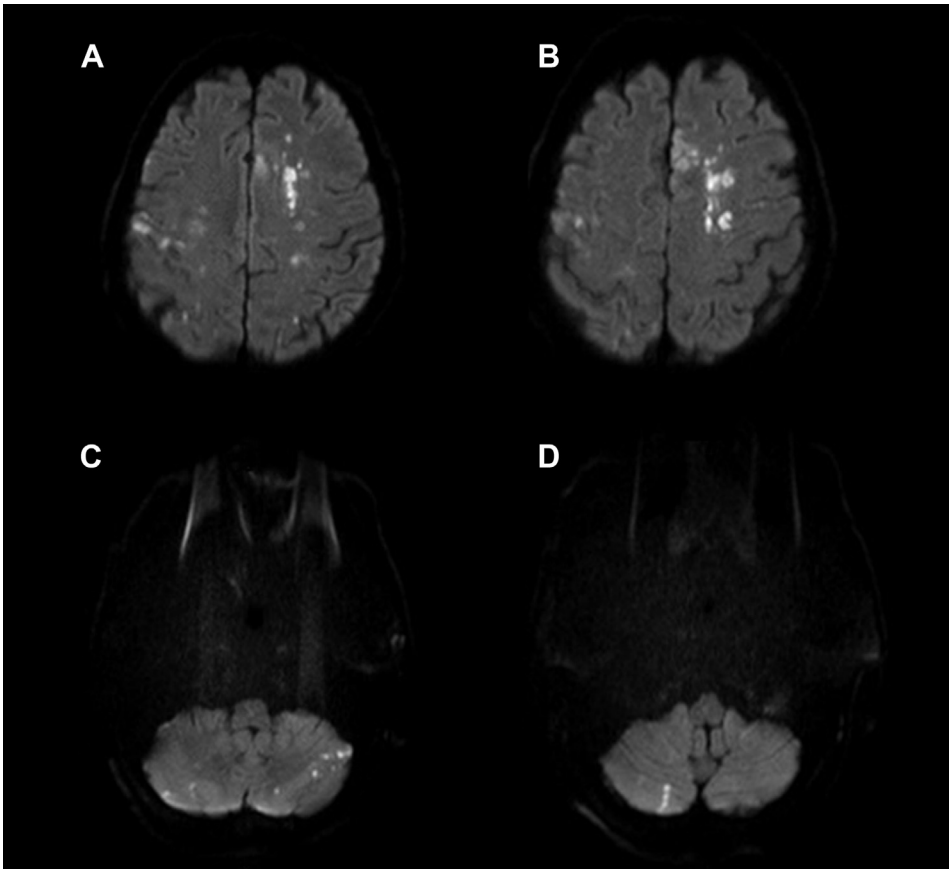

Figure 2. Diffusion-weighted images showed multiple areas of restricted water diffusion in (A, B) the bilateral cerebra and (C, D) the cerebella, findings consistent with embolic infarcts.

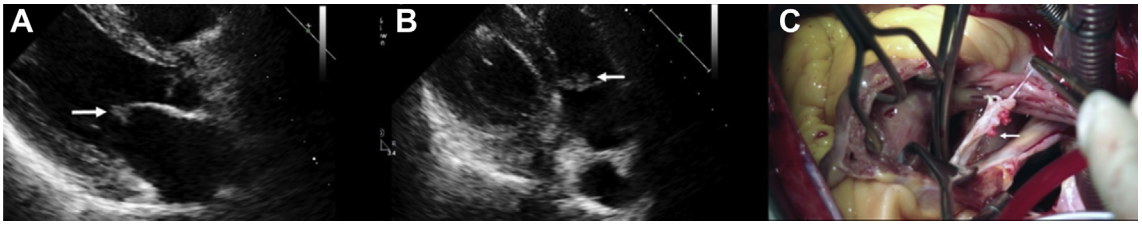

Figure 3. Transthoracic echocardiogram illustrating (A) mitral valve and (B) tricuspid valve vegetations. (C) The small pink vegetation represents a typical finding with nonbacterial thrombotic endocarditis without valve destruction.

splenic and renal infarcts and recurrent tumor. However, the serology study was negative for all parameters assessed (normal values of protein C, protein S, antithrombin III, and lupus anticoagulant antibodies).

The definitive diagnosis of NBTE can be made by demonstrating the presence of platelet thrombi on autopsy or surgical specimens. In clinical practice, a diagnosis of NBTE depends on a constellation of clinical and echocardiographic findings, as well as an absence of microbiologic findings. Typically, the demonstration of valvular vegetations on echocardiography in the absence of systemic infection in patients who are at high risk of NBTE provides strong evidence to support the diagnosis [8]. In our case, cancer-related NBTE was proven based on a high level of CA-125, CT findings consistent with recurrent tumor (Figure 1C) with embolic infarcts (Figure 1B), serial negative blood cultures, negative cultures of the surgical samples, typical transthoracic echocardiogram (Figure 3A), and surgical specimens (Figure 3C).

Unlike infective endocarditis, NBTE has a higher potential for embolization due to limited cellular organization and mobile properties [7]. Systemic embolism occurs in 14–91% of NBTE cases and usually affects cerebral, coronary, renal, and mesenteric circulation [3,9]. In our case, the patient was diagnosed with stroke-in-evolution, bilateral renal infarction, and splenic infarctions by imaging modalities.

It is critically important to distinguish between NBTE and infective endocarditis, because these conditions have different therapeutic plans. The diagnosis of infective endocarditis is based on clinical, microbiologic, and echocardiographic findings together with Duke's criteria [10]. The treatment approach for patients with infective endocarditis includes appropriate antibiotic treatment with consideration of valve replacement if heart failure or uncontrolled infection occurs, as well as treatment for the prevention of embolic events [11]. The application of cardiac surgery in NBTE is controversial; however, in our case, valve replacement was strongly

indicated because of the severe dysfunction (severe mitral valve regurgitation and tricuspid valve regurgitation), stroke prophylaxis, and possible infective endocarditis [12].

Treatment of patients with NBTE is challenging, and therapeutic goals are typically directed at curing the underlying malignancy and systemic anticoagulation. Monotherapy with vitamin K antagonists in patients with malignancy-associated NBTE is not recommended because recurrent thromboembolic events have been commonly observed in patients receiving warfarin alone [13]. In our case, we initially administered an antiplatelet drug and vitamin K antagonist (warfarin) for stroke prevention. Stroke-in-evolution was noted on neurological examination, with symptoms of acalculia, mutism, and recent memory impairment, followed by the onset of motor aphasia and decline in muscle power in the right limbs. The patient immediately received a heparin infusion, and the symptoms quickly improved. Dual anticoagulation therapies were necessary due to the hypercoagulable state of OCCC-related NBTE. Therefore, chemotherapy should be initiated immediately if the patient has a good performance status.

In conclusion, our case report underscores that NBTE should be considered among the possible causes of multifocal embolic infarctions and as an early manifestation of OCCC recurrence. Dual anticoagulation therapy with heparin and warfarin is necessary to reduce the risk of recurrent thromboembolism. Recurrent OCCC with NBTE and systemic embolisms can cause morbidity and mortality if diagnosis is delayed. Early recognition, together with appropriate clinical management, can improve the patient's quality of life and prognosis.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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