Case Report

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Spontaneous arterial thrombosis in a patient with advanced ovarian clear cell cancer: a case report and literature review

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Abstract

Patients with ovarian cancer are often in a hypercoagulable state and have a high risk of venous thrombosis, including deep vein thrombosis and pulmonary embolism. However, arterial thrombosis is relatively rare in ovarian cancer. We report a case a 46-year-old woman with ovarian clear cell carcinoma who developed arterial and venous thrombosis in the lower extremities as the first manifestation. Her arterial thrombosis-related ischemic symptoms were not responsive to anticoagulant treatment of low-molecular-weight heparin, but improved after neoadjuvant chemotherapy and surgery. Therefore, we hypothesize that the optimal therapy for arterial thrombosis in ovarian cancer is treatment for the underlying disease (i.e., ovarian cancer). A thorough investigation is required to determine the relationships between arterial thrombosis and ovarian cancer and antithrombotic treatments for ovarian cancer related-arterial thrombosis.

Keywords

Ovarian clear cell cancer, arterial thrombosis, venous thromboembolism, antithrombotic treatment, low-molecular-weight heparin, CA125, chemotherapy

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Introduction

Ovarian cancer is identified as one of the types of cancer with the highest risk of venous thromboembolism (VTE).[1] A recent retrospective study of 328 patients with ovarian cancer showed that the incidence of VTE was up to 39.3%.[2] A prospective study, which focused on VTE at the time of diagnosing ovarian cancer with systemic screening for symptomatic and asymptomatic cases, reported that the incidence of ovarian cancer-related VTE was 22.7%.[3] Moreover, compared with other histological types, ovarian clear cell carcinoma (OCCC) is more prone to thrombosis.[4] Despite the association between VTE and ovarian cancer, data on arterial thromboembolism (ATE) in ovarian cancer are relatively rare.

ATE is generally observed in atherosclerosis and related to rupture of an unstable atherosclerotic plaque.[5] However, increasing evidence has shown that unprovoked ATE may occur before overt malignancy. A cohort study of 6600 patients with lower limb arterial thrombosis showed that this population had a higher risk of a subsequent diagnosis of cancer, especially during the first 6 months of follow-up for ATE, compared with the general population.[6] This finding suggested that lower limb ATE was a marker of increased risk for occult cancer. Furthermore, lower limb ATE was considered as an adverse prognostic factor for mortality in common cancers, such as colon, lung, urinary bladder, and breast cancer, except for prostate cancer, whereas ovarian cancer was not included in this study.[6] Aikou et al. investigated the association between ATE in cerebral arteries and ovarian cancer in 827 patients with ovarian cancer, and showed a low incidence (3.2%) of cerebral infarction in ovarian cancer.[7] Interestingly, there was a significant relationship between cerebral infarction and OCCC compared with other types of ovarian cancer.[7] However, there is a lack of studies concerning ovarian cancer-related ATE, especially in the extremities. To the best of our knowledge, there has been only one previous case in which a patient with ovarian cancer had ATE in the upper extremities as the first manifestation.[8]

We report a patient who was diagnosed with OCCC who initially presented with ATE and VTE in the lower extremities. We also review the incidence, risk factors, underlying mechanisms, and treatment of ATE in ovarian cancer.

Case report

A 46-year-old nulliparous woman originally presented at the Vascular Surgery Department with complaints of unbearable sharp pain and severe swelling in the right leg. This swelling occurred 4 months previously and gradually became severe over this period of time. The sharp pain was aggravated for 10 days before presentation, and it had disturbed her walking ability. Her right foot was cyanotic and the right dorsalis pedis had no palpable pulse. The patient denied having a personal or family history of thrombosis or malignancies and her body mass index was 21.8 kg/m^2. Ultrasonography showed a completely thrombosed great saphenous vein and femoral vein of the right leg, as well as a partially thrombosed popliteal vein of the left leg. Subsequent computed tomography (CT) angiography showed thrombi extending from the right common iliac artery to the right internal iliac artery, the right lower femoral artery, and both sides of the popliteal artery (Figure 1). We incidentally discovered a large pelvic mass.

The patient was then treated with low-molecular-weight heparin (LMWH) for nearly 2 weeks, resulting in alleviated swelling. However, the pain still existed and the right foot remained cold and cyanotic.

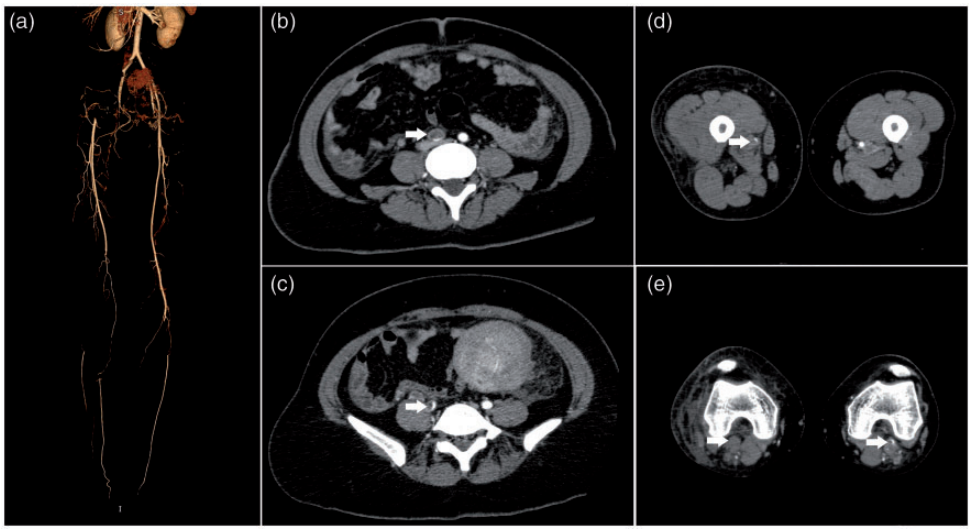

Figure 1. Computed tomography angiogram of the patient. (a) Arterial thrombosis in the lower extremities can be seen. Thrombi in the right common iliac artery (b), the right internal iliac artery (c), the right lower femoral artery (d), and both sides of the popliteal artery (e) can be seen. White arrows indicate thrombi in arteries.

Because of the large pelvic mass discovered by computed tomography angiography, the patient was recommended to contact a gynecologist. Laboratory analyses showed an elevated D-dimer level (6.56 mg/L) and platelet count (972×10^9/L), and elevated levels of several serum tumor markers (cancer antigen [CA] 199: 150.1 U/mL, CA125: 736.5 U/mL, CA153: 71.9 U/mL, CA724: 54.2 U/mL, neuron specific enolase: 38.7 ng/mL, and CA242: 69.9 U/mL). The possibility of malignancy led to further diagnostic work-up using fluorine-18 fluorodeoxyglucose positron emission tomography/CT (Figure 2). This technique showed a 109.3×68.9-mm cystic-solid mass with increased fluorodeoxyglucose activity in the right pelvic cavity, and an inhomogeneously thickened abdominal and pelvic peritoneum, omentum, and capsule of the liver and spleen with increased fluorodeoxyglucose uptake. These findings suggested disseminated ovarian cancer with metastasis in the abdomen and pelvis, while ascites was also observed in the abdominal and pelvic cavities. Subsequently, CT-guided biopsy of the pelvic mass confirmed the presence of OCCC (Figure 3).

Accordingly, she underwent three cycles of neoadjuvant chemotherapy every 3 weeks with docetaxel and carboplatin. This was followed by a considerable decrease in the CA125 level (177.6 U/mL), platelet count (503×10^9/L), and D-dimer level (1.29 mg/L). Surprisingly, cyanosis of her right foot and pain in the right leg became less severe, although she was still unable to walk. After neoadjuvant chemotherapy, interval debulking surgery was conducted including hysterectomy, salpingo-oophorectomy, omentectomy, partial ureterectomy, pelvic peritonectomy, mesenteric lymphadenectomy of the small intestine, and resection of lesions on the left paracolic sulcus, ileocecal mesentery, and ileal and descending colon surface. During surgery, we observed massive yellowish ascites of nearly 2000 mL. This

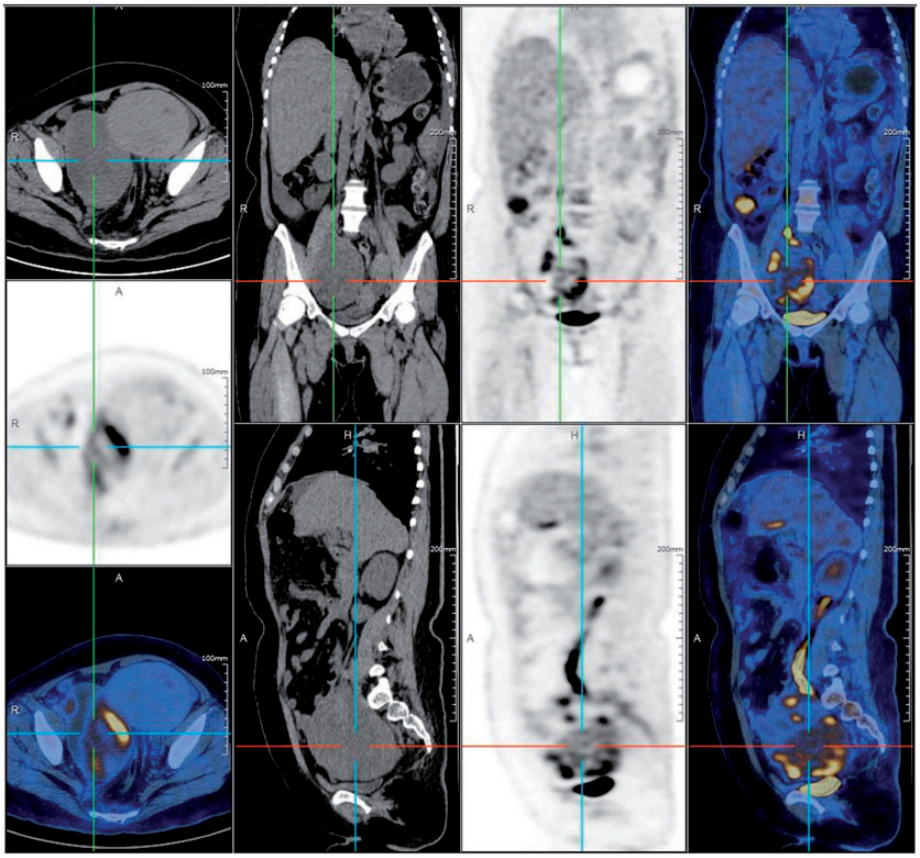

Figure 2. Positron emission tomography/computed tomography shows disseminated ovarian cancer with metastasis in the abdomen and pelvis.

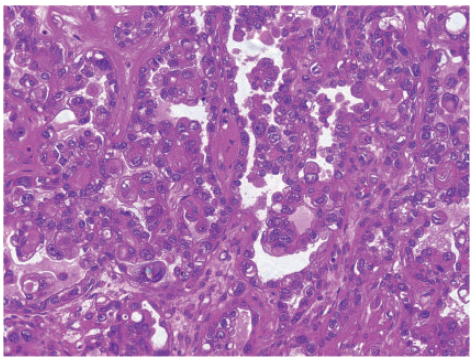

Figure 3. Tissue stained with hematoxylin and eosin from a computed tomography-guided biopsy of the pelvic mass. Ovarian clear cell carcinoma with a hobnail growth pattern can be seen (200× microscopic view).

surgery reached optimal debulking with no macroscopic residual lesions and led to a lower CA125 level (64.2 U/mL). Three cycles of the same chemotherapy every 3 weeks were continued after surgery, followed by a normalized CA125 level (10 U/mL), D-dimer level (0.19 mg/L), and platelet count (141×10^9/L).

After all of the anti-cancer treatments, the patient's foot was free of cyanosis and the pain was relieved, which eventually allowed the patient to walk unaided. A follow-up ultrasound showed thrombosis in the right superficial femoral artery, popliteal artery, and posterior tibial artery, and recanalization of thrombi in the left

posterior tibial artery and dorsal artery of the left foot. During follow-up, anticoagulation was continued with Rivaroxaban (20 mg once a day) for longer than 1 year.

This study was performed in compliance with the EQUATOR Network guidelines. The study was approved by the ethic review committee of Zhongshan Hospital Affiliated to Fudan University. Written informed consent for publication was obtained from the patient and her parents.

Discussion

Ovarian cancer is associated with a higher incidence of VTE than other types of cancer.[9] A large pelvic tumor or massive ascites compressing the intrapelvic veins, immobility, pelvic surgery, and platinum-based chemotherapy may contribute to an increased risk of VTE in ovarian cancer.[10] Although the relationship between ovarian cancer and VTE has been well established, ATE is relatively rare in patients with ovarian cancer. A study that focused on thrombotic events in ovarian cancer showed that the incidence of cerebral infarction and acute myocardial infarction was 2.2% and 0.3%, respectively, which was lower compared with that of VTE (14.4%).[4]

Arterial thrombosis frequently occurs in patients with atherosclerosis, and may develop in any vessels, leading to myocardial infarction, ischemic stroke, and ischemic symptoms in the extremities. However, an increasing amount of evidence has indicated unprovoked arterial thrombosis in patients with cancer. Recently, in a population-based study of 374,331 pairs of patients with cancer and matched controls, the risk of ATE increased by nearly 70% in 360 days before a diagnosis of cancer compared with cancer-free controls.[11] Additionally, the respective relative risks of myocardial infarction and ischemic stroke were similar.[11] A prospective, observational cohort study showed that 2.6% of patients with cancer developed ATE, including myocardial infarction, stroke, and peripheral artery disease.[12] These arterial thrombotic events were related to a three-fold increased risk of mortality compared with patients without ATE. Similarly, another study showed that the 30-day cumulative incidence of death after ATE, defined as myocardial infarction or ischemic stroke, was 17.6% in patients with cancers versus 11.6% in controls.[13]

Development of ATE is multifactorial. The classical risk factors for arterial disease in the heart, brain, and extremities include smoking, arterial blood pressure, and serum cholesterol levels, which may lead to damage in the arterial wall, systemic inflammation, and coagulation.[14] Obesity, diabetes, pregnancy, combined oral contraceptives, and oral hormone replacement therapy also increase the risk of ATE.[14]

Cancer itself might be an independent risk factor for ATE. Vavlukis et al. reported a female patient who was diagnosed with gastric carcinoma and originally presented with ATE in the right lower extremity.[15] In another report, a female patient had aortic thrombus from the infrarenal abdominal aorta to the right common iliac artery, and was then discovered to have early esophageal cancer.[16] Additionally, the risk of ATE varies by type of cancer, with lung, gastric, and pancreatic cancers having the highest risk, and this risk steadily rises with increasing stages of cancer.[13] A previous study that evaluated the association between ATE and advanced cancer stage showed that 40% of patients with cancer with preceding ATE were diagnosed at stage III or IV.[11] The authors of this study concluded that lung and colorectal cancer were the most likely cancers to be preceded by ATE.

There is partial overlap between risk factors for ATE and cancer. Common conditions, such as obesity, diabetes, hypertension, and dyslipidemia, may

account for development of ATE and cancer by inducing inflammation.[17] A retrospective study considered a body mass index >23 kg/m^2, hypertension, cerebrovascular disease, arterial fibrillation, increased aspartate transaminase levels, and stage IV as significant predictors for ATE in patients with pancreatic cancer.[18] In a population-based cohort study on ischemic stroke in ovarian cancer, age ≥50 years, hypertension, and diabetes were regarded as independent risk factors for an arterial thrombotic event.[19] Furthermore, this previous study also showed that patients with ovarian cancer who received platinum-based chemotherapy were at high risk for stroke. Grilz et al. reported that cancer treatments, such as platinum-based chemotherapy and radiotherapy, contributed to the occurrence of ATE in cancer.[12] Angiogenesis inhibitors added to therapy of ovarian cancer also increase the risk of ATE.[20]

The exact mechanisms of cancer-associated ATE remain unclear. Cancer is characterized by a hypercoagulable and procoagulant state through interaction with platelets and secretion of procoagulant substances, which increase the risk of ATE in patients with cancer.[13] An increased platelet count is commonly observed in several cancers, such as cancer of the lung, ovary, endometrium, rectum, kidney, stomach, pancreas, brain, and breast.[21] Tumor cells can directly induce platelet activation and aggregation, which is called tumor-cell induced platelet aggregation. Tumor-cell induced platelet aggregation is directly triggered by overexpressed podoplanin in tumor cells via binding to C-type lectin-like receptor 2 on the platelet's surface. Additionally, tissue factor expressed on the tumor cell surface generates thrombin, thereby activating platelets.[21] With regard to an indirect manner, tumor cells lead to platelet activation by releasing microvesicles with tissue factor into the bloodstream.[22] Another indirect way to activate platelets is through formation of neutrophil extracellular traps, which are released from neutrophils stimulated by tumor-derived granulocyte colony-stimulating factor.[23] The relationship between platelets and cancer is bidirectional. Platelets are crucial for cancer cell proliferation, angiogenesis, and invasiveness. Egan et al. conducted an *in vitro* study and reported that activated platelets induced pro-survival and pro-angiogenic signals for ovarian cancer cells.[24] Platelets also increase invasion potential and induce epithelial to mesenchymal transition in ovarian cancer, thus promoting metastasis.[25] Furthermore, circulating tumor cells enveloped by platelets can avoid an attack of natural killer cells and high shear stress in the bloodstream.[21] Another mechanism of arterial thrombosis relates to vascular toxicity associated with anti-cancer therapies. Soultati et al. concluded that vascular endothelial growth factor inhibitors and platinum-based agents may place patients at high risk of thrombosis through induction of endothelial apoptosis and proinflammatory cytokines.[26]

We experienced a rare case of a patient with OCCC who initially presented to hospital because of symptoms of arterial and venous thrombosis in the right lower extremity. Nevertheless, we failed to demonstrate a causal relation between them. In a retrospective study that recruited 5717 patients with active cancer and VTE, the authors concluded that arterial ischemic events occurred early after VTE, and were a major complication in patients with VTE and active cancer.[27] VTE and ATE have a close interrelationship and share common risk factors, such as older age, increased oxidative stress, and a systemic inflammatory response. However, the exact underlying mechanisms of this relationship are still uncertain. Our patient had no risk factors for thrombosis, including smoking, obesity, diabetes, and atherosclerosis. Because of discovery of the pelvic mass in our patient,

the diagnosis of venous and arterial thrombosis and the increased levels of several tumor markers indicated the possibility of malignancy. Compared with other histological types, OCCC has a higher incidence of thromboembolic events, including venous and arterial thromboembolic events.[4,28] OCCC has been identified as a risk factor of thromboembolic events.[4] In a recent guideline, LMWH was recommended for the initial and long-term management of cancer-associated VTE, while direct oral anticoagulants can be used for early maintenance and long-term management of VTE in cancer.[29] Antiplatelet therapies, such as aspirin and oral $P2Y_{12}$ inhibitors, play a vital role in treating arterial thrombosis. Additionally, regular use of low-dose aspirin was reported to reduce the risk of overall cancer, especially gastrointestinal tract tumors.[30] However, there is a lack of consensus on clinical treatment for cancer-associated ATE, which may be attributed to the paucity of randomized, controlled trials.

Our patient achieved relief from swelling after anticoagulant therapy with LMWH for almost 2 weeks, whereas the ischemic symptoms and signs were still present, including sharp pain, a cyanotic right foot, and a decreased pulse in the dorsalis pedis. After surgery and chemotherapy, the ischemic symptoms improved. This finding indicated that routine anticoagulant treatment with LMWH may not be sufficient, and that optimal therapy for ATE in ovarian cancer may be treatment for the underlying disease (i.e., ovarian cancer). However, OCCC can show resistance to conventional chemotherapy,[31] and recurrence may develop via microscopic tumor foci that are not affected by cytotoxic drugs because of subclinical small ATE. Therefore, there is an urgent need to investigate the role of antithrombotic reagents in ovarian cancer-associated ATE, especially OCCC.

In conclusion, patients who suffer from arterial thrombosis without atherosclerosis and other ATE risk factors should undergo further evaluations because of the possibility of cancer. Antithrombotic treatments for ATE accompanied by OCCC should involve both anticoagulant and anti-cancer therapy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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