Case Reports in Women's Health 37 (2023) e00485

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

Right middle cerebral artery stroke secondary to ovarian clear cell carcinoma in a 35-year-old: A case report

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ARTICLE INFO

Keywords:
Arterial thrombosis
Endometriosis
Venous thromboembolism
Case report
Ovarian cancer

ABSTRACT

Thromboembolic events (TEEs) can be classified into two types: venous TEEs (vTEEs), such as pulmonary embolism (PE) and deep vein thrombosis (DVT), and arterial TEEs (ATEs), such as acute myocardial infarction and cerebral infarction. Ovarian cancer has a high incidence of venous thromboembolism, with the clear cell subtype carrying the highest risk. However, the incidence of ATEs, especially cerebral infarction, in patients with ovarian carcinoma, of all subtypes, is much lower. This report is of a rare case of a 35-year-old Asian woman who presented with sudden onset of left hemiplegia and right gaze as the first presenting signs of an underlying ovarian malignancy. The patient had no pertinent medical history and no underlying cardiovascular risk factors. Final diagnosis was stage 2B clear cell carcinoma of the ovary without lymphovascular invasion arising from endometriosis. Patients who suffer from arterial thrombosis without known atherosclerotic risk factors should undergo further evaluations to rule out the possibility of cancer, particularly ovarian carcinoma.

1. Introduction

The association between malignancy and thromboembolic events (TEEs) is well studied. Specifically, gynecologic malignancies have been associated with venous TEEs (vTEE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Among epithelial ovarian tumors, histologically, clear cell carcinoma shows the strongest association with vTEEs, with the risk estimated to be 11–27% [1]. However, the incidence of arterial thromboembolic events (ATEs) in patients with ovarian carcinoma, of all subtypes, is much lower, at 2.4%, with the incidence of cerebral infarction reported most recently at 2.2% [2]. Moreover, ATEs almost always occur in the setting of significant cardiovascular disease, with fewer than 10% of patients having no known etiology [3].

There have been reports of cerebral infarctions in patients with ovarian cancer that may have been caused by nonbacterial thrombotic endocarditis, a pre-existing hyper-coaguable condition, or in the presence of a patent foramen ovale [4]. In a study of 827 patients with epithelial ovarian cancer, only 27 patients (3.2%) presented with cerebral infarction, with only 1.7% of patients presenting prior to treatment [5]. However, there has been only one previous published case in which a patient with no underlying cardiovascular risk factors had a cerebral infarction as the first manifestation of clear cell carcinoma of the ovary [4]. This case report is of a 35-year-old patient who was diagnosed with ovarian clear cell carcinoma who initially presented with arterial thromboembolism in the right middle cerebral artery.

2. Case Presentation

A 35-year-old woman, G1P1, presented to the emergency department after she became suddenly slumped over, with right gaze and left hemiplegia. The initial computerized tomography (CT) scan of the head was negative for a cerebral bleed or cerebral vascular accident; however, a CT perfusion study showed a thrombus in the M1 segment of the middle cerebral artery (MCA) (Fig. 1). She received tissue plasminogen activator and mechanical thrombectomy resolved her neurological symptoms. Four days later, the patient began to have recurrent left-sided

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https://doi.org/10.1016/j.crwh.2023.e00485
Received 29 January 2023; Received in revised form 4 February 2023; Accepted 7 February 2023
Available online 10 February 2023

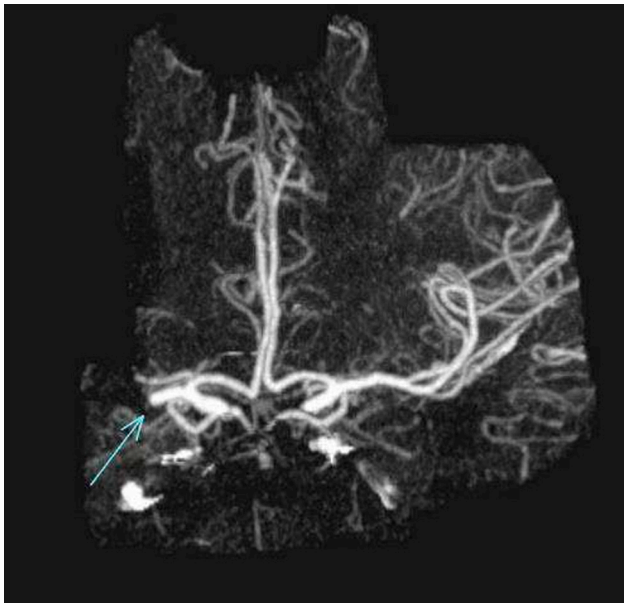

Fig. 1. CT perfusion study showing thrombus in M1 segment of the middle cerebral artery.

hemiplegia and was taken to the operating room where she underwent right-sided hemicraniectomy for treatment of malignant edema from the right MCA stroke. Postoperatively, the patient was managed in the intensive care unit, where her course was complicated by anemia requiring transfusion, in addition to a 3.7 cm scalp abscess requiring incision and drainage and intravenous antibiotics. Full anti-coagulation following thrombectomy was maintained with enoxaparin 1 mg/kg subcutaneous injections twice a day.

The patient's medical history was significant for hypertension during pregnancy, which was additionally complicated by post-partum hemorrhage. Elevated blood pressures had persisted for 3.5 years since the delivery; however, she was not on any medication. She had not seen a gynecologist since the delivery of her child. She had normal menstrual cycles, denied significant gynecologic history (including endometriosis), and denied any use of oral contraceptives or smoking. The patient's family history was noncontributory.

Initial workup for a thrombotic event was negative. Her electrocardiogram was normal, with no evidence of atrial fibrillation. Her cardiac Doppler ultrasound scan was unremarkable and demonstrated no intra-atrial communication or intracardiac thrombi that would demonstrate a patent foramen ovale or bacterial thromboembolism, respectively. Doppler scans were negative for deep vein thrombosis on her initial admission. Laboratory tests were all normal on admission, including calcium of 9.3 and platelet count of 255. She had multiple negative COVID-19 tests and denied any recent history of COVID-19 infection. She had not received any COVID-19 vaccine. Hyper-coagulable work-up was all within normal limits.

On hospital day 6, the patient underwent extensive imaging including a CT scan and subsequent Ultrasound of the abdomen and pelvis that demonstrated a complex pelvic cystic mass measuring up to 10x7cm (See Fig. 2). The right-sided component measured approximately 6.3 × 3.6 cm and the left, fatty component measured 8 × 5.7 cm. Her CA-125 was 308.

Gynecology oncology was consulted and recommended surgical management. The patient underwent aggressive stroke rehabilitation, and was transferred a month later to a tertiary institution for definitive operative management of a pelvic mass concerning for malignancy. Enoxaparin was discontinued 24 h prior to exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and paraaortic lymph node dissection. The final diagnosis

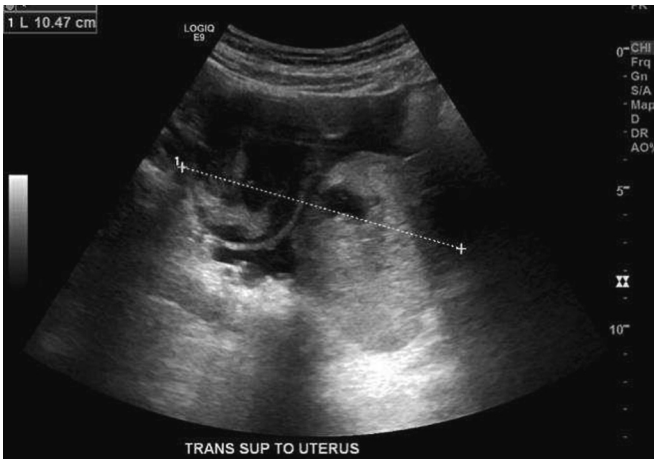

Fig. 2. Transvaginal ultrasound demonstrating pelvic cystic mass.

was stage 2B clear cell carcinoma of the ovary without lymphovascular invasion arising from a background endometriosis (See Fig. 3). Anti-coagulation was re-started 12 h after surgery. The patient was discharged home on enoxaparin 1 mg/kg sub-cutaneous injections twice a day and transitioned to apixaban 5 mg twice-a-day 1 month later.

The patient completed dose-dense paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 followed by carboplatin AUC 5 day 1 repeated every 21 days for 6 cycles, as per the National Comprehensive Cancer Network guidelines. She continued to have residual left upper and lower extremity weakness and sensory deficits. Two years after initial diagnosis, she radiologically and clinically had no evidence of malignancy disease and her most recent CA-125 was 6.

3. Discussion

There are multiple histologic subtypes of ovarian cancer, including high- and low-grade serous, clear cell, endometrioid and mucinous [6], each with its own distinct disease pattern and cell biology. Ovarian clear cell carcinoma (OCCC) is a rare histologic type, accounting for approximately 3.7–12.1% of all epithelial ovarian carcinomas [7]. Clinical characteristics that differentiate OCCC are presentation as a large, unilateral pelvic mass, association with a history of endometriosis, association with hypercalcemia and high VTE complication risk [7].

Although this patient denied any clinical history of endometriosis, on histologic examination of specimen her OCCC was found to arise from

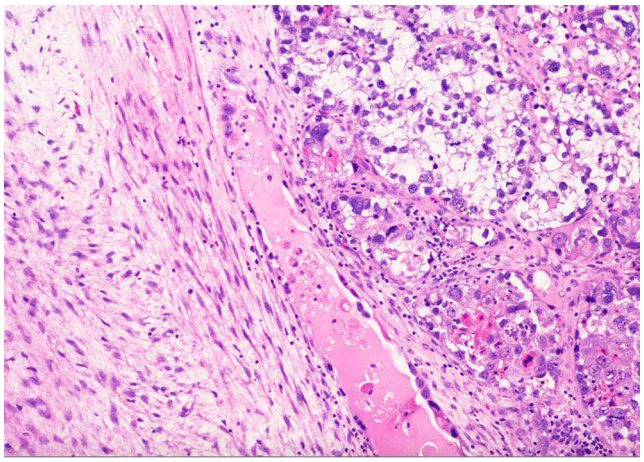

Fig. 3. Histology slide 10×. Clear cell carcinoma has solid, diffuse pattern and it is showing polygonal cells with abundant clear cytoplasm due to glycogen content.

endometriosis. According to the literature, the risk of ovarian cancer among women with endometriosis is increased by 30–40%. Specifically, endometrioid cancer followed by clear cell carcinoma represents the most known examples of an epithelial malignancy arising from endometriosis [8]. Endometriosis has also been identified as a novel independent risk factor for VTE (OR 2.70, 95% CI 1.21–6.00) [9]. Recently, endometriosis has been found to increase arterial stiffness and thus patients may be at increased cardiovascular risk [10]. However, research specifically looking at the risk of ATE in patients with endometriosis is lacking.

There are many mechanisms to explain why ovarian cancer is associated with a higher incidence of VTE than other types of cancer. This includes a large pelvic tumor or massive ascites compressing the intrapelvic veins, immobility, pelvic surgery, and platinum-based chemotherapy [11]. Additionally, tissue factor, cancer procoagulant, and inflammatory cytokines such as interleukin 6 (IL-6) all play a role in the mechanism of the hyper-coagulable state associated with ovarian carcinoma [12]. Specifically, clear cell carcinoma has been shown to produce excess levels of tissue factor and IL-6 and is thus more likely to lead to the development of VTE [12].

However, an increasing amount of evidence has indicated that spontaneous arterial thrombosis is increased in patients with cancer. A recent study of 374,331 patients with cancer with matched controls found that the risk of arterial thromboembolic events begins to increase 150 days before the date of cancer diagnosis and peaks in the 30 days before [13]. However, this study only included patients over the age of 67 and those diagnosed with breast, lung, prostate, colorectal, bladder, non-Hodgkin lymphoma, uterine, pancreatic or gastric cancers. Thus, the applicability of this study to ovarian cancer is unknown.

The historic risk factors for ATE in the heart, brain, and extremities include smoking, elevated arterial blood pressure, and serum cholesterol levels which can lead to hypercoagulation, systemic inflammation and damage to the endothelial lining of the arterial wall. Additionally, obesity, diabetes, pregnancy, combined oral contraceptive, and oral hormone replacement therapy also increase the risk of ATE. There is a need to determine if and how cancer itself is an independent risk factor for ATE, specifically looking at subtypes of ovarian cancer.

It has been found that cerebrovascular events can be the first manifestation of cancer. In one study, out of 5106 patients admitted for ischemic stroke, 24 patients (0.4%) had an underlying malignancy. Out of these 24, only two patients had ovarian cancer (8%). The primary mechanisms underlying the strokes were found to be non-bacterial thrombotic endocarditis (NBTE) (8/24), diffuse intravascular coagulation (DIC) (6/24) and atherosclerosis (5/24) [14].

In this case, the neurologist and hematologist tried to determine an underlying etiology of her ATE, but could not find an underlying cause or mechanism. This patient was found to have no evidence of NBTE, DIC, or risk factors for atherosclerosis. There have been prior case reports of patients with NBTE presenting with stroke as their first presenting sign of ovarian cancer, one with high-grade serous [15] and two with ovarian clear cell adenocarcinoma [16,17]. Additionally, there have been prior case reports of patients with ovarian clear cell carcinoma presenting with a cryptogenic stroke from a patent foramen ovale [18] or simultaneously with a DVT [19]. In the two cases that have been previously reported describing stroke alone as the first manifestation of ovarian clear cell carcinoma, one patient had significant ATE risk factors, including hypertension and diabetes, and the second patient was 55 years old and the time from stroke to initial diagnosis was 4 months [4].

4. Conclusion

In conclusion, patients who suffer from arterial thrombosis without atherosclerosis and other ATE risk factors should undergo further evaluations to rule out the possibility of cancer, particularly ovarian clear cell carcinoma.

Contributors

Pegah Blustein contributed to drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Sarah Werner contributed to patient care, conception of the case report, drafting the manuscript, and revising the article critically for important intellectual content.

Sunder Sham contributed to data acquisition and revising the article critically for important intellectual content.

Anthony Febles contributed to patient care, data acquisition, and revising the article critically for important intellectual content.

Heather Katz contributed to patient care, conception of the case report, and revising the article critically for important intellectual content.

Jeannine Villella contributed to patient care, conception of the case report, and revising the article for important intellectual content.

All authors approved the final submitted manuscript.

Funding

No funding was received for this project.

Patient consent

Written informed consent for publication of their details and images was obtained from the patient prior to the writing of this case report.

Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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