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Case report

Correction of coagulopathy associated with non-bacterial thrombotic endocarditis (NBTE) by surgical debulking in a case of ovarian clear cell carcinoma

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1. Introduction

Systemic hypercoagulability is a complication of malignancy, with up to 10% of ovarian cancer patients developing venous thromboembolism (VTE) (Abu Saadeh et al., 2013). In cancer patients, the presence of deep vein thrombosis (DVT) or pulmonary embolism (PE) is associated with increased risk of readmission and death (Levitan et al., 1999). Additionally, non-cancer patients presenting with VTE are five times as likely to be subsequently diagnosed with cancer (Baron et al., 1998). The hypercoagulable state of malignancy is related to a combination of procoagulant factor expression, cytokine secretion, alterations to the endothelium, and consequences of treatment (e.g. immobilization, surgery, chemotherapy) (Falanga et al., 2013).

Although the most common complication from cancer-related hypercoagulability is VTE, the risk extends to arterial thromboses (el-Shami et al., 2007). Non-Bacterial Thrombotic Endocarditis (NBTE) is a condition whereby, in absence of infection, thrombi of platelets and fibrin are deposited on cardiac valves, with potential for systemic embolization.

2. Case

A 61 year-old woman with a known 4.1 cm ascending aortic aneurysm, aortic valve regurgitation, and migraine headache with aura presented to the emergency department reporting acute onset of burning, right lower quadrant abdominal pain radiating to her right flank, and nausea without emesis. She also reported severe headache with aura and photophobia, lightheadedness, and blurry vision, as well as generalized malaise and urinary incontinence over the preceding 2–3 weeks.

On presentation, she was afebrile with a blood pressure of 117/61, pulse of 79, respiratory rate of 16, and oxygen saturation of 99% on room air. Physical examination revealed right-sided lower abdominal tenderness. A CT scan demonstrated a 12 cm complex cystic pelvic mass, splenic and renal infarcts, and ascites. Initial labs revealed WBC 12,800/uL, Hgb of 13.7 g/dL, hematocrit of 42.2% and platelet count of 225,000/uL.

On hospital day 1, the abdominal pain improved, however, she reported left substernal chest pain. An electrocardiogram revealed a non-ST elevated myocardial infarction (NSTEMI) with elevated troponins, peaking at 1.67 ng/mL. A transthoracic echocardiogram revealed a stable dilated ascending aortic aneurysm and severe aortic regurgitation, with preserved ejection fraction of 65%. A CT scan of the head showed focal areas of hypoattenuation concerning for underlying ischemic infarcts, though neurological exam remained non-focal. Tumor markers were notable for elevated serum CA125 to 69 U/mL, serum CA19-9 elevated to 284 U/mL, and normal CEA of 1.7 ng/mL. The patient's platelet count dropped to 109,000/uL.

On hospital day 2, the patient complained of shortness of breath with pleuritic chest pain. A thoracic CT angiogram revealed bilateral segmental and subsegmental PEs. She was started on therapeutic heparinization. The patient's platelet count dropped to 47,000/uL. A heparin-induced thrombocytopenia (HIT) panel was negative. On hospital day 3 the patient reported transient visual field deficits, and right upper extremity weakness; CT and MRI of the brain revealed multiple, scattered acute and subacute ischemic infarcts as well as foci of subarachnoid hemorrhage. The heparin drip was discontinued and the patient underwent IVC filter placement.

On hospital day 4, the patient developed word finding difficulties, right upper extremity weakness. Worsening ischemia and subarachnoid hemorrhages were seen on a repeat brain MRI. Coagulation studies revealed platelets of 37,000/uL, INR of 1.13, and PTT of 35.2 s. An infusion of 1 pack of platelets did not yield an appropriate rise. In the context of multiple embolic infarcts, the thrombophilia was thought to be consumptive in etiology. There was a high suspicion for NBTE.

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In light of the patient's worsening status, interdisciplinary discussions were held. She was a poor candidate for aortic valve replacement, as she would be unable to be anticoagulated during the procedure due to intracranial hemorrhages. The decision was made to remove the ovarian mass in hopes of reversing the coagulopathy.

The next morning, on hospital day 5, her platelets were 36,000/uL, improving to 86,000/uL with an infusion of 1 pack of platelets. She underwent an exploratory laparotomy, bilateral salpingo-oophorectomy, and an omental biopsy with an estimated blood loss of 100 mL. An intraoperative transesophageal echocardiogram revealed vegetations on all three aortic valve leaflets consistent with NBTE. She received two additional units of platelets during surgery with improvement to 124,000/uL post-operatively. A frozen section of the ovarian mass was consistent with a clear cell adenocarcinoma of the ovary. Given the thrombophilia, additional staging was not performed. After the procedure she remained intubated and was sent to the Surgical Intensive Care Unit.

On postoperative day 1 she was extubated and found to have extensive bilateral DVT, further evolution of ischemic infarcts, and a new 7 mm cerebellar parenchymal hemorrhage. After reaching a nadir hematocrit of 20.1%, she was transfused 2 units of packed RBC with recovery to 24.8%. Over the next two days, her hematocrit recovered to 28.5%, her platelets stabilized at 168,000/uL, and repeat CT showed no further embolic or hemorrhagic events. However, her respiratory status worsened despite diuresis and she was re-intubated on postoperative day 3. She developed supraventricular tachycardia and was started on an amiodarone drip. An echocardiogram demonstrated a decrease in her ejection fraction from 65% to 28%.

She then began a slow and steady cardio-pulmonary, hematologic, and neurologic recovery. She was extubated on postoperative day 7, restarted on a heparin drip on postoperative day 13, and transitioned to enoxaparin injections two days later. On postoperative day 17, she was discharged home in good condition. Final pathology showed FIGO Stage IA ovarian clear cell carcinoma. One week after discharge she was started on adjuvant carboplatin and paclitaxel.

After 6 cycles of carboplatin and paclitaxel her CA-125 level had decreased to 7 U/mL, her follow-up echocardiogram revealed an ejection fraction of 55%, and a CT scan of her abdomen and pelvis showed no evidence of disease. She then underwent a completion of staging (hysterectomy, pelvic and para-aortic lymph nodes, omentectomy, and directed biopsies), which revealed no evidence of disease on final pathology. She remains with no evidence of disease 9 months from her original diagnosis.

3. Discussion

We present an unusual case of a patient with an ovarian clear cell carcinoma, presenting with systemic vascular dysfunction in the form of DVT, PE, ischemic and hemorrhagic stroke, and myocardial, renal, and splenic infarcts, all in the context of NBTE and consumptive and non-infectious DIC.

The differential diagnosis of acute, widespread arterial infarction includes: VTE through a patent foramen ovale, cardiac thrombus secondary to arrhythmia or malfunction, plaque embolization in atherosclerosis, endocarditis, and various hypercoagulable states including DIC, antiphospholipid syndrome, and HIT. Although rare, NBTE should be considered early in a patient with manifestations of arterial infarction such as stroke, myocardial infarction, or hematuria. In our patient, transthoracic echocardiogram found no evidence of a patent foramen or mural thrombus. She remained afebrile with negative cultures and a mild WBC elevation, so suspicion for infectious endocarditis or DIC was low, and the coagulopathy preceded the introduction of heparin. Considering the patient's known aortic root aneurysm, clinical suspicion centered on NBTE.

NBTE has no official diagnostic criteria, and refers to valvular lesions of varying underlying etiology, in the absence of systemic infection. The incidence of NBTE at autopsy ranges from 0.9–2.3%, with over 60% of cases associated with underlying malignancy (Deppisch & Fayemi, 1976; Rosen & Armstrong, 1973). Coexisting coagulation abnormalities including thrombocytopenia, prolongation of PT, and depression of fibrinogen are common (Rosen & Armstrong, 1973). Arterial thromboembolism is the primary health risk from NBTE and occurs in about 50% of patients (el-Shami et al., 2007). The most common neoplasms associated with NBTE are pancreatic, lung, and stomach cancers, with the strongest histological association being adenocarcinoma (Deppisch & Fayemi, 1976; Rosen & Armstrong, 1973). Mucin secreted by tumor cells has been speculated to play a role in development of NBTE in some cases (Min et al., 1980).

Recommendations for treatment of malignancy associated NBTE include therapeutic anticoagulation with heparin, and treatment of the underlying malignancy. Warfarin has been found to be ineffective at preventing recurrent thromboembolic events in NBTE (el-Shami et al., 2007), while factor Xa and thrombin inhibitors remain largely unstudied. Valvular surgery is only indicated in cases with concomitant heart failure. In the setting of worsening DIC, we proceeded with surgical removal of the ovarian mass.

In a study of the Medicare population, ovarian cancer patients showed the highest rate of malignancy-associated DVT or PE (Levitan et al., 1999). Ovarian clear cell carcinoma has an incidence of VTE ranging from 27–42%, with odds ratio of 2.5–5.2 relative to other epithelial ovarian cancers (Duska et al., 2010; Matsuura et al., 2007). NBTE has been described previously in association with multiple gynecologic malignancies (Delgado & Smith, 1975), but most often with ovarian cancer. Of four cases of NBTE identified in association with ovarian clear cell carcinoma, two presented during metastatic recurrence (Devulapalli et al., 2012; Yilmaz et al., 2015), and two during primary presentation of the malignancy (Oueida & Scola, 2011; Aryana et al., 2006).

In conclusion, we present a rare case of coagulopathy and NBTE as the primary presentation of early stage ovarian clear cell carcinoma. NBTE is a rare paraneoplastic syndrome associated with a wide variety of malignancies and often presents with systemic emboli. We demonstrated that the otherwise refractory coagulopathy can be reversed by surgical removal of the mass.

Conflicts of interest

The authors have no conflicts to report.

Informed consent

Permission was obtained from the patient prior to preparation of the manuscript.

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