Case report

Nonbacterial thrombotic endocarditis with embolic cerebral vascular accidents in a patient with advanced, recurrent clear cell carcinoma of the ovary: A case report

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1. Introduction

Nonbacterial thrombotic endocarditis (NBTE) is characterized by deposition of sterile platelet and fibrin thrombi on valvular structures, which are prone to embolism and most commonly involve the cerebral circulation (González et al., 1991; Sørensen et al., 2000). NBTE is not uncommon in patients with advanced mucin-secreting ovarian adenocarcinomas, and a few case reports have shown an association with ovarian clear cell cancer (OCCC) (Heit et al., 2000; Aryana et al., 2006; Devulapalli et al., 2012; Naoi et al., 2013). In North America and Europe, OCCC is the second most common histologic subtype of epithelial ovarian cancer, with an estimated prevalence of 1–12% (Goff et al., 1996). Advanced OCCC carries a poor prognosis and is associated with an elevated risk of vascular thrombotic events, with as many as 40% of patients experiencing thromboembolic events (Goff et al., 1996). Here we report on a patient with metastatic OCCC presenting with embolic cerebrovascular accidents (CVAs) while on treatment for recurrent disease.

2. Case

A 68-year-old Caucasian female developed shortness of breath in May 2010. Computed tomography (CT) of the chest, abdomen and pelvis revealed a pulmonary embolus (PE) in the right lower lobe pulmonary artery, a 16.6 × 13.1 cm pelvic mass, retroperitoneal lymphadenopathy, right pleural effusion, and a right pleural-based mass measuring 1.8 × 1.3 cm. CA-125 tumor marker was elevated at 358 U/mL. The patient was placed on dalteparin for PE management.

One month later she underwent exploratory laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral ureterolysis, para-aortic lymph node dissection, ablation of diaphragmatic nodules, and liver right lobe wedge resection. Pathology revealed stage IVB OCCC. Of note, the patient underwent prophylactic inferior vena cava filter placement preoperatively and was started on enoxaparin following complete gross surgical debulking.

Following surgery, the patient enrolled in Gynecologic Oncology Group (GOG) 252, a phase III trial of bevacizumab with intravenous (IV) versus intraperitoneal (IP) chemotherapy, and received six cycles of IP carboplatin at an area under the curve (AUC) of 6 on day 1 and weekly IV paclitaxel 80 mg/m² on days 1, 8, and 15. With the start of cycle 2 she also received IV bevacizumab at 15 mg/kg once every 3 weeks. After the last dose of combination chemotherapy, the patient was maintained on IV bevacizumab at 15 mg/kg once every 3 weeks for a total of 16 additional cycles, which she completed in 12/2011.

One month after completion of maintenance bevacizumab therapy, CT revealed progression of disease in liver segment 4B and the right pleura. The patient underwent a video-assisted thoracoscopic surgery (VATS), thoracic lymphadenectomy, open celiac lymphadenectomy, and partial hepatectomy. Postoperatively, it was recommended that she restarts enoxaparin, but she elected to forego further anticoagulation therapy. Following secondary debulking, the patient was treated with weekly paclitaxel and investigational VTX-2337 from 8/2012 to 11/2012, followed by carboplatin and liposomal doxorubicin from 11/12 to 2/13, and gemcitabine and bevacizumab in 3/13, but her disease continued to progress.
echocardiogram (TEE) revealed a 1.8 × 0.8 cm mass on the anterior
leaflet of the mitral valve that was immobile and situated on the atrial side of the valve. It was well circumscribed with mild-to-moderate mitral valve regurgitation. Serial blood cultures to rule out infective endocarditis were negative. NBTE was suspected, and the patient was started on enoxaparin 60 mg SQ BID.

Repeat brain MRI 2 weeks after initial presentation revealed evolving subacute infarcts in the right greater than left occipital lobes, parietal lobes, posterior corpus callosum, and posterior mesial temporal lobes. The patient’s vision and memory improved gradually, but never returned to baseline. A cardiac MRI revealed normal left ventricular size and an EF of 69%. Follow-up TTE revealed an EF of 65% and thickened mitral valve leaflets that opened well.

The patient re-initiated systemic therapy for advanced OCCC with pemetrexed and bevacizumab followed by irinotecan and bevacizumab, but unfortunately, her OCCC continued to progress. While on palliative therapy for progressive disease, the patient remained on enoxaparin and did not experience further embolic neurologic complications. The patient died from end-stage OCCC 7 months following her NBTE diagnosis.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient values</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>4.7 × 10^9 cells/μL</td>
<td>3.9–10.7 × 10^9 cells/μL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.9 g/dL</td>
<td>12–16 g/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>68 × 10^3 /μL</td>
<td>150–450 × 10^3 /μL</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>3.52</td>
<td>1.5–8.0 (1500 to 8000/mm³)</td>
</tr>
<tr>
<td>BUN</td>
<td>19 mg/dL</td>
<td>7–18 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 mg/dL</td>
<td>0.6–1.2 mg/dL</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.4 mEq/L</td>
<td>3.5–5.0 mEq/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>138 mEq/L</td>
<td>135–145 mEq/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.5 mEq/L</td>
<td>1.5–2.0 mEq/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.8 mg/dL</td>
<td>8.4–10.2 mg/dL</td>
</tr>
<tr>
<td>PT</td>
<td>14.0 s</td>
<td>11–13 s</td>
</tr>
<tr>
<td>INR</td>
<td>1.14</td>
<td>0.8 to 1.2</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>8.6 mg/dL</td>
<td>&lt;0.5 mg/dL</td>
</tr>
<tr>
<td>ESR</td>
<td>15 mm/h</td>
<td>0–20 mm/h</td>
</tr>
<tr>
<td>LDL</td>
<td>98 mg/dL</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>187 pg/mL</td>
<td>200–800 pg/mL</td>
</tr>
<tr>
<td>Folate</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>2.33 uU/mL</td>
<td>0.5–4.6 uU/mL</td>
</tr>
<tr>
<td>CA125</td>
<td>914 U/mL</td>
<td>&lt;35 U/mL</td>
</tr>
</tbody>
</table>

WBC, white blood cell count; BUN, blood urea nitrogen; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; ESR, erythrocyte sedimentation rate; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

In April 2013, 6 weeks after her last dose of bevacizumab, the patient presented with a 3-day history of headaches and sudden onset visual changes. She described “blobs” in her visual field and impairment in her peripheral vision. Within hours, she developed confusion, with the inability to remember any events of the prior 24 h. Neurological exam revealed a left homonymous hemianopsia and retrograde short-term memory loss. She was afebrile and her vital signs revealed: pulse 96, blood pressure 139/56, respiratory rate 20, and oxygen saturation 100% on room air. Her laboratory values were significant for elevated C-reactive protein and CA-125 as well as low Vitamin B12 and hemoglobin (Table 1).

Non-contrast CT of the brain revealed an area of low attenuation with mild mass effect within the right occipital region consistent with an acute infarct. Brain magnetic resonance imaging (MRI) with and without gadolinium revealed acute infarcts in the right greater than left occipital lobes, parietal lobes, posterior corpus callosum, and posterior mesial temporal lobes. The patient’s vision and memory improved gradually, but never returned to baseline. A cardiac MRI revealed normal left ventricular size and an EF of 69%. Follow-up TTE revealed an EF of 65% and thickened mitral valve leaflets that opened well.

### 3. Discussion

Thrombosis constitutes the most frequent complication and second most common cause of death in cancer patients, with the emergence of thromboembolic disease occasionally preempts the diagnosis of malignancy, as first noted by Trousseau in 1865 (Zacharski et al., 1983; Rickles & Edwards, 1983). Malignancy promotes a prothrombotic state in patients via aberrant production of tissue factor and cancer procoagulant, such as interleukin 1β (IL-1β), tumor necrosis factor alpha (TNF-α), and vascular endothelial growth factor (VEGF) (Dranoff, 2004). TNF-α and IL-1β derived from malignant cells can induce endothelial cells to increase tissue factor procoagulant activity and to produce the fibrinolysis inhibitor plasminogen activator inhibitor 1. This accelerates the prothrombotic potential of endothelial cells in malignancy. (Lee & Levine, 1999).

It is the hypercoagulable state of malignancy that is thought to permit NBTE, (Aryana et al., 2006) a non-infectious endocarditis characterized by thrombi composed of immune complexes, mononuclear cells, and fibrin. NBTE more commonly involves the mitral (64%) and aortic (25%) valves (Steiner, 1993), and is a complication that is mainly but not exclusively associated with advanced malignancy. In a prospective study of 200 cancer patients, echocardiographic evidence of NBTE was identified in 19%, a prevalence 10 times higher than that of the control population (Aryana et al., 2006). NBTE vegetations are prone to embolization and can involve multiple organ sites simultaneously. The most common sites of embolization are the cerebrovascular, coronary, splenic, pulmonary, and renal circulations (Aryana et al., 2006).

Cancer therapeutics can also enhance hypercoagulability. Our patient received bevacizumab as part of her adjuvant and maintenance
therapy along with anticoagulation therapy. However, after her second debulking she discontinued anticoagulation therapy and received multiple systemic chemotherapy regimens including bevacizumab, which in the absence of anticoagulation therapy may have contributed to hypercoagulability and NBTE. Bevacizumab in particular has been associated with arterial thromboembolism, and to a lesser extent venous thromboembolism, in the setting of malignancy (Nalluri et al., 2008).

Bevacizumab, a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human VEGF has been shown to increase the risk of arterial thromboembolism when administered with chemotherapy. In a study of 1745 patients with metastatic breast, colorectal, or non-small cell lung carcinoma treated with bevacizumab and chemotherapy versus chemotherapy alone, the chemotherapy plus bevacizumab cohort had a significantly increased risk of developing arterial thromboembolism compared to the chemotherapy-only group (Zacharski et al., 1983).

Treatment of NBTE consists of both anticoagulation and anti-cancer therapy. Both IV and subcutaneous unfractionated heparin therapy have been found to be effective in reducing the incidence of recurrence of NBTE. Low-molecular-weight heparin may also be used, although there is less evidence for its long-term efficacy (el-Shami et al., 2007). Vitamin K antagonists are less effective in controlling malignancy-associated NBTE (Aryana et al., 2006; el-Shami et al., 2007). The effectiveness of newer anticoagulants such as factor Xa and direct thrombin inhibitors remains to be established. In this patient with prior PE, continuation of anticoagulation therapy could have prevented the development of NBTE.

Adenocarcinoma of the ovary has been described as a cause for NBTE, but OCCC presenting with NBTE is very rare. There are only three published case reports on NBTE in OCCC. Systemic embolization from NBTE to pulmonary, coronary, splenic, and renal territories as presenting sequelae in a patient with stage IIC OCCC and without pulmonary metastatic disease (Zacharski et al., 1983) should be considered in all OCCC patients presenting with multiple embolic events.

**Conflict of interest statement**

The authors have no conflicts of interest to disclose.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

**References**


