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Case Report

Vertebral artery dissection and cerebral infarction in a patient with recurrent ovarian cancer receiving bevacizumab☆

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Case history

The patient is a 60-year-old woman with stage IIIC ovarian cancer who underwent primary optimal cytoreductive surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and lymphadenectomy in 2010. She was then randomized to Arm I of GOG 252 and received a total of six cycles of dose dense weekly intravenous (IV) paclitaxel 80 mg/m^2 with IV carboplatin Area under Curve (AUC) 6.0 every 21 days and IV bevacizumab 15 mg/kg every 21 days starting with cycle 2. She completed an additional six cycles of bevacizumab maintenance but was subsequently removed from the study due to disease progression by both CA125 and computed tomographic (CT) imaging. She was then started on oral cyclophosphamide 50 mg daily with bevacizumab 10 mg/kg IV every 2 weeks and had a great response as indicated by serial CA125 monitoring. Of note, the patient had a history of chronic hypertension which preceded her diagnosis of her ovarian cancer and was not exacerbated by her treatment with bevacizumab; her blood pressures remained well controlled on stable doses of enalapril and hydrochlorothiazide (HCTZ).

Following cycle 9 of this regimen, she experienced an acute "snap" in her neck with associated sudden onset vertigo, left-sided headache, slurred speech and ataxia as well as nausea, emesis and diarrhea. There was no antecedent trauma, cervical strain, or torque. She was transported via ambulance to her local emergency department for evaluation, where admission vital signs were within normal limits and physical exam was remarkable for intact cranial nerves and no focal neurologic signs. A head CT without contrast revealed no acute abnormality and admission laboratories, including complete blood count (CBC), complete metabolic panel (CMP), cardiac enzymes and toxicology screen that were within normal limits.

However, magnetic resonance imaging (MRI) of the brain with and without contrast revealed an acute medial left posterior inferior cerebellar artery (PICA) territory infarct with abnormal signal intensity within the left vertebral artery wall suggestive of dissection (Fig. 1). A CT angiogram of the cervical and intracranial vasculature confirmed a proximal left vertebral artery dissection with severe areas of narrowing (Fig. 2). A transthoracic echocardiogram revealed normal cardiac function and no source of embolism. During this admission, the patient's chronic hypertension remained controlled with her home medications, including enalapril and HCTZ, and she was started on clopidogrel antiplatelet therapy and rosuvastatin for hyperlipidemia management.

Her neurologic symptoms began to improve with intensive inpatient rehabilitation and she is currently able to perform her activities of daily living without difficulty. Three month follow-up CT angiogram demonstrated evolution of the vertebral artery dissection into a proximal occlusion. While this finding poses a low risk for future ischemic events, she will continue indefinitely on antiplatelet therapy and continue with aggressive management of her hypertension and hyperlipidemia. With regards to her malignancy, she has remained without evidence of disease (NED) despite stopping bevacizumab treatment.

Discussion

Bevacizumab is a humanized monoclonal anti-vascular endothelial growth factor (VEGF) antibody with reported clinical benefit in the primary (Burger et al., 2011) and secondary (Burger et al., 2007; Cannistra et al., 2007) treatments of ovarian cancer. While generally well tolerated, bevacizumab has several adverse events (AEs) which can limit its use in ovarian cancer patients (Randall and Monk, 2010). Arterial thromboembolic events (ATEs), including myocardial infarction and cerebrovascular accident (CVA), have been associated with the use in ovarian cancer patients albeit with a reported low incidence ranging 0 to 3% (Randall and Monk, 2010). ATEs have also been reported with

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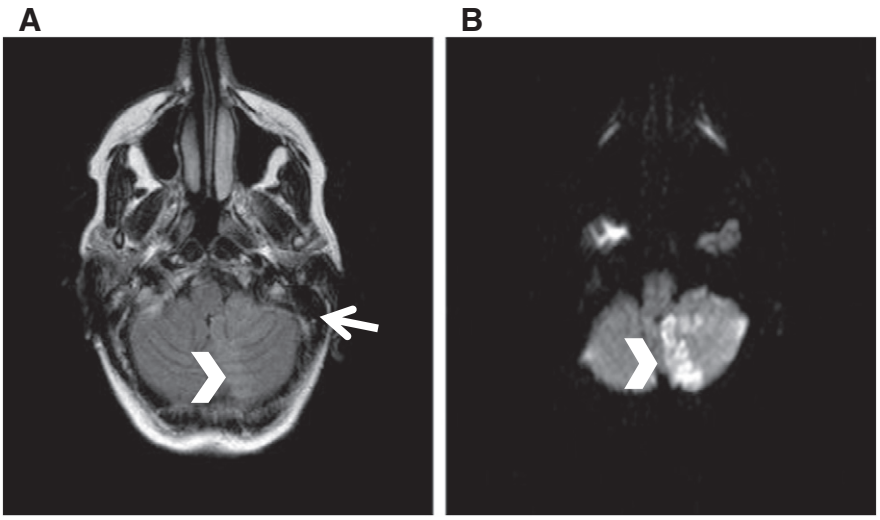

Fig. 1. A. Axial FLAIR image demonstrates abnormal signal intensity (arrowhead), representing subacute infarction in the distribution of the left posterior inferior cerebellar artery, in the medial inferior left cerebellum extending to the cerebellar tonsil. There is a suggestion of wall thickening/intramural hematoma (arrow) within the distal left vertebral artery. B. Axial diffusion weighted image demonstrates hyperintensity (arrowhead) in the same region.

bevacizumab use in patients with other primary tumors (Scappaticci et al., 2007). In a post hoc analyses of 5 randomized controlled trials including 1745 patients with metastatic colorectal, breast or non-small cell lung cancers, combination therapy with bevacizumab and chemotherapy (compared to chemotherapy alone) was associated with an increased risk of ATEs (hazard ratio (HR) 2.0, 95% confidence interval (CI) = 1.05 to 3.75, $p = 0.031$) as well as an increase in the absolute rate of developing an ATE (5.5 vs. 3.1 events per 100 person-years, respectively, for combination therapy vs. chemotherapy alone; HR 1.8, 95% CI = 0.94 to 3.33, $p = 0.076$). In this analysis, ATE development was significantly associated with prior ATEs ($p < 0.001$) or age ≥65 years ($p = 0.01$); of note, our patient did not have either of these risk factors.

Cerebrovascular events attributed to bevacizumab treatment are infrequently reported in the literature, likely stemming from their overall low incidence. In a single institution review, 10 patients were identified with bevacizumab-associated cerebrovascular events, including intratumoral hemorrhage (n = 7), cerebral watershed infarction (n = 1), transient ischemic attack (n = 1) and left vertebral artery occlusion (n = 1) (Seet et al., 2011). Patients were treated with bevacizumab over a median duration of 3 months (range 2–4 months) for various primary tumors, including primary brain malignancies (n = 5), non-small cell lung cancer (n = 2), renal cell carcinoma (n = 1), colorectal cancer (n = 1) and recurrent angiosarcoma (n = 1). While 4 patients experienced modest recovery, six patients died within 3 months of their cerebrovascular events, emphasizing that this type of ATE is a serious AE associated with bevacizumab.

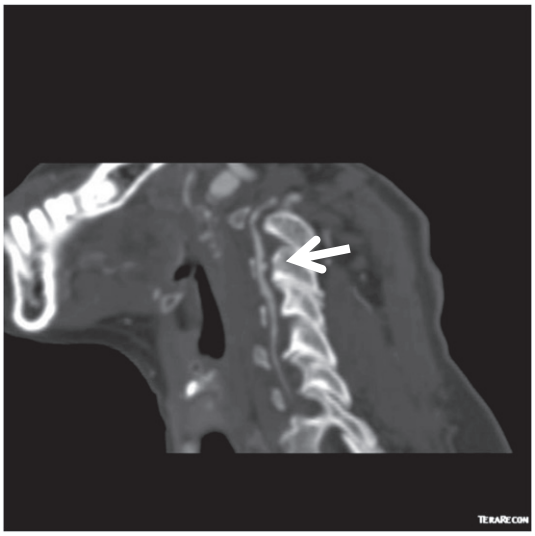

Fig. 2. Curved reformatted image from CT angiogram demonstrates irregularity and narrowing of the mid cervical left vertebral artery, reconstituted at the C6 level with small pseudoaneurysm (arrow) projecting posteriorly at the C3 level. Findings are consistent with arterial dissection.

In addition to her acute PICA CVA, our patient also had evidence for a left vertebral artery dissection, an AE not previously reported with bevacizumab. Spontaneous arterial dissection is a leading etiology of ischemic strokes in patients younger than 45 years of age and accounts for up to 2% of all ischemic strokes (Fusco and Harrigan, 2011). Vertebral arterial dissection classically presents with neck or head pain followed by posterior cerebral ischemia (Fusco and Harrigan, 2011); our patient presented with both of these findings. A key anatomic feature of vertebral artery dissections is intimal disruption, a condition which promotes intramural hematoma formation and increases the risk of thromboembolic stroke (Fusco and Harrigan, 2011). While our patient has additional risk factors for stroke including hypertension and hyperlipidemia, bevacizumab may have contributed to her vertebral artery dissection (and subsequent posterior cerebral infarction) by impairing VEGF-mediated endothelial repair; it was therefore eliminated as a treatment of her recurrent ovarian cancer.

Digital subtraction angiography (DSA) is the gold standard imaging study for vertebral artery dissection; however, MRI and CT angiography (CTA) are acceptable alternatives. DSA not only can identify common findings of dissection including eccentric, smooth or irregularly tapered stenosis and intraluminal thrombus but can also identify rare pathognomonic features such as an intimal flap or double lumen (Fusco and Harrigan, 2011). Common findings of dissection seen on MRI and CTA are a crescent-shaped intramural hematoma (Goldberg et al., 1986) and an eccentric arterial lumen with mural thickening, respectively. In our patient, suspicious findings on MRI triggered further evaluation with a CTA which confirmed the vertebral artery dissection.

Spontaneous dissections are often medically managed with antithrombotic therapy, including antiplatelet agents or anticoagulants. Thrombolytic agents have been utilized in the treatment of acute ischemia associated with dissection-mediated thromboembolism (Fusco and Harrigan, 2011). The role of endovascular therapy, including stents and grafts, remains controversial; treatment is often reserved for those patients with symptomatic and enlarging dissections on surveillance

imaging (Fusco and Harrigan, 2011). In general, patients with dissections have a good prognosis, with the majority of lesions resolving within three to six months following the injury (Gonzales-Portillo et al., 2002) and 50% of patients experiencing recanalization of their occlusions (Redekop, 2008). Our patient was treated with clopidogrel alone, given an allergy to aspirin, and bevacizumab was discontinued. Three months following her dissection and CVA, she continues to show significant improvement in her neurologic status corresponding with findings on her surveillance imaging.

In summary, bevacizumab is known to increase the risk of arterial thromboembolic events (Randall and Monk, 2010) and may have contributed to the development of this patient's vertebral artery dissection and cerebrovascular accident. Bevacizumab should be used with caution in patients older than 65 years and/or those with prior ATEs or conditions predisposing them to ATEs (Randall and Monk, 2010). Further, clinicians should also educate their patients about the risk of ATEs associated with bevacizumab, regardless of risk factors, as early recognition of ATE-related symptoms is likely to result in improved patient outcomes.

Conflict of interest statement

The authors attest that there are no conflicts of interests.

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