

CLINICAL CASE CHALLENGES

A Unique Case of Orthostasis in a Patient With Testicular Choriocarcinoma



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CASE

A 24-year-old male undergoing treatment for metastatic testicular choriocarcinoma presented to the cardio-oncology clinic with a 2-week history of nausea/vomiting and orthostasis.

Four months prior, this previously healthy patient was diagnosed with a heterogenous solid testicular mass with central cystic change via ultrasound after presenting with scrotal swelling. He had no allergies, no daily medicines, and no contributory family history. Two weeks after his testicular ultrasound, he presented to the emergency room with headaches and right hemianopsia. Brain computed tomography (CT) and subsequent magnetic resonance imaging showed a single 2.7 cm × 1.7 cm left occipital lobe brain metastasis, and he was admitted for further evaluation and management. Alpha-fetoprotein, lactate dehydrogenase (LDH), and human chorionic gonadotropin (HCG) levels were <2 ng/ml (N), 295 U/l (H), and 17,750 U/l (H), respectively, suggestive of a germ cell tumor. He underwent orchiectomy, which revealed pathology-proven choriocarcinoma. Staging CT revealed lung metastases. Prior to starting chemotherapy, pulmonary function tests showed minimal obstructive defect.

The patient was subsequently started on bleomycin, etoposide, and cisplatin therapy (BEP). In the setting of his intracranial metastasis, the potential pulmonary toxicity of BEP was preferred over the increased risk of thrombocytopenia and potential for intracranial hemorrhage with the alternative regimen of etoposide, ifosfamide, and cisplatin (VIP). His first cycle of therapy was complicated by atrial fibrillation with rapid ventricular response as well as nausea and vomiting. He converted to normal sinus rhythm with amiodarone, metoprolol, and diltiazem, and then transitioned to diltiazem XR 240 mg daily without further palpitations. He was not started on anticoagulation due to his low CHA₂DS₂-VASC score and his intracranial metastasis. Transthoracic echocardiogram (TTE) demonstrated mild right ventricle and left atrium dilation and left ventricular hypertrophy. Lower extremity venous Dopplers were normal. After his first cycle of BEP, his right-sided peripherally inserted central catheter was removed prior to discharge. He then received outpatient gamma knife radiosurgery and dexamethasone taper for the brain metastasis.

Cycle 3 was again complicated by significant nausea/vomiting, and olanzapine was added to his regimen. After the third cycle, tumor markers were HCG 22 IU/l and LDH 524 U/l, which his oncology team felt were reassuring due to significant decrease in HCG.

His fourth cycle was again complicated by significant nausea/vomiting requiring intermittent fluid boluses for profound orthostasis. Brain magnetic resonance imaging reassuringly demonstrated interval decrease in brain tumor size.

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He returned to the cardio-oncology clinic on the last day of his cycle 4 bleomycin treatment having received a fluid bolus 2 days prior. Orthostatic vital signs were profoundly positive with unmeasurable blood pressure upon standing, and he quickly laid down to avoid syncope and then began vomiting. The physical examination was otherwise unremarkable. Laboratory evaluation included a hemoglobin of 11.7 g/dl, normal electrolyte panel, LDH 489 U/l, and HCG 9.5 IU/l, indicating that the cancer was responding well to chemotherapy. A repeat staging CT scan was planned for the next week.

WHAT WOULD YOU DO NEXT?

- a. In-office fluid bolus
- b. Start fludrocortisone
- c. Repeat brain imaging
- d. Admit to the hospital

b. The patient was started on fludrocortisone 0.1 mg daily to improve fluid retention, because fluid boluses were providing only transient benefit. Diltiazem dose was halved, but not abruptly stopped to avoid rebound tachycardia. Orthostasis was attributed to hypovolemia secondary to chemotherapy side effects. Orthostatic precautions were emphasized. The plan was to add midodrine and completely stop diltiazem if orthostasis persisted.

A chest CT scan obtained 1 week later showed filling defect in the superior vena cava, 3.5 cm × 4.1 cm right atrium (RA) mass, bilateral pulmonary emboli, and an interval decrease in the known pulmonary nodules. There was no evidence of new metastatic disease. The patient experienced some improvement with his medication changes but remained symptomatic with orthostasis.

WHAT WOULD YOU DO NEXT?

- a. Add midodrine and refer to outpatient cardiothoracic surgery.
- b. Add midodrine and start anticoagulation.
- c. Admit to the hospital for further evaluation of the mass.
- d. Stop diltiazem. Hold anticoagulation given prior brain metastasis. Schedule close follow-up CT scan.
- e. The patient was admitted and options were discussed between oncology, neurosurgery, and cardio-oncology. It was agreed to initiate anticoagulation despite the patient's history of brain metastasis. Given the RA mass's size and its location obstructing tricuspid valve inflow, the mass was felt to be the cause of his orthostasis. Thrombus was felt to be the most likely etiology in view of his recent port. Although LDH remained high and tumor thrombus associated with germ cell tumor including an RA mass has been reported, tumor thrombus was felt to be less likely given normalization of HCG and generally favorable response of his tumor on CT (1).

TTE immediately after admission revealed a 3.6 cm × 2.5 cm rounded mass. Features of the mass on TTE remained concerning for potential tumor on review with a senior echocardiographer.

WHAT WOULD YOU DO NEXT?

- a. Cardiac magnetic resonance imaging (CMR)
 - b. Anticoagulation with subsequent repeat imaging
 - c. Thrombolysis
 - d. Surgical excision of the mass
 - e. Positron emission tomography scan
- a. CMR was performed to better characterize the mass and guide treatment options. CMR illustrated a homogenous 4.5 cm × 4.0 cm mass extending into the RA appendage, and post-contrast images showed a homogenous nulling of the mass (Figure 1). These findings were consistent with a thrombus.

ABBREVIATIONS AND ACRONYMS

BEP = bleomycin, etoposide, and cisplatin

CT = computed tomography

HCG = human chorionic gonadotropin

ICH = intracranial hemorrhage

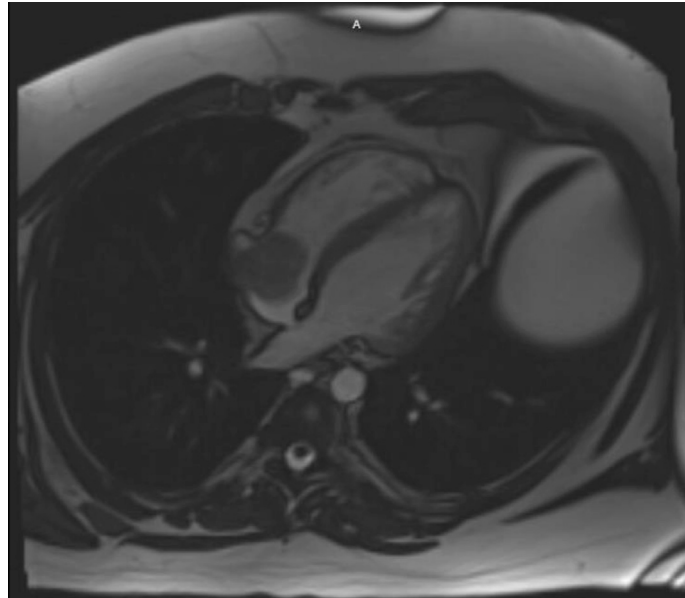
LDH = lactate dehydrogenase

RA = right atrium

SVC = superior vena cava

TTE = transthoracic echocardiogram

VTE = venous thromboembolism

FIGURE 1 Cardiac Magnetic Resonance Image of the Right Atrial Mass

This gadolinium-enhanced cardiac magnetic resonance image confirms thrombus as opposed to tumor thrombus due to homogenous nulling (darkness) of the mass.

HOW WOULD YOU TREAT THIS ATRIAL THROMBUS?

- a. Anticoagulation
 - b. Thrombolysis
 - c. Open surgical thrombectomy
 - d. Endovascular thrombectomy
 - e. Monitor clinically
- d. Endovascular thrombectomy. Thrombolysis and/or thrombectomy were considered given the extensive clot burden and large atrial thrombus likely obstructing cardiac flow. Thrombolysis was felt contraindicated due to known brain metastasis. Endovascular thrombectomy (AngioVac, Angiodynamics, Latham, New York) or open surgical approach were considered the best options. Endovascular approach was chosen, as it was thought to be less invasive and had lower associated morbidity than an open approach. AngioVac thrombectomy using a right internal jugular vein approach was performed with near complete removal of the RA thrombus. Post-operative recovery was uneventful; the patient was started on apixaban 10 mg twice daily for 1 week followed by 5 mg twice daily thereafter. At discharge, his orthostatic symptoms had resolved, and follow-up imaging revealed no residual mass.

DISCUSSION

Our patient presented with significant orthostasis resulting from a large RA thrombus obstructing his right ventricular inflow. His orthostatic symptoms completely resolved after removal of the clot with endovascular thrombectomy. This case highlights the importance of a multidisciplinary approach for patients with cancer, the utility of magnetic resonance imaging for tissue characterization, and the potential advantage of endovascular thrombectomy in patients with contraindications to thrombolysis.

Chemotherapy commonly causes nausea/vomiting and associated orthostasis. Symptoms are generally managed with antiemetics and fluid boluses. There are no guidelines for orthostatic hypotension, although the American College of Cardiology's guidelines for related vasovagal syncope recommends midodrine (Class IIa) and fludrocortisone (Class IIb) among other options (2). Fludrocortisone was prescribed here because the

primary etiology was felt to be hypovolemia; midodrine, considered as potential add-on therapy, would be preferred for vasodilation.

Subsequent CT imaging revealed the cause of his orthostasis to be a large RA thrombus obstructing his right ventricular inflow with bilateral pulmonary emboli and superior vena cava thrombus potentially contributing as well. Cancer is a major risk factor for venous thromboembolism (VTE), with a 4 to 7 times relative risk when compared with the general population (3). Thrombotic events can be common and, in fact, are the second leading cause of death in certain cohorts of patients undergoing outpatient chemotherapy (4). Our patient's risk for VTE was increased by higher cancer stage, chemotherapy regimen (cumulative incidence of VTE on cisplatin is 12.2%), and prior right-sided intravenous port (5).

Although the initial CT was suggestive of RA thrombus, extensive metastatic disease or tumor thrombus could not be excluded. Choriocarcinoma can metastasize directly through the blood to the lungs; at least 1 case report has detailed metastatic choriocarcinoma with tumor thrombus in the RA and pulmonary vessels diagnosed with F-18 fluorodeoxyglucose positron emission tomography (1,6). As tumor thrombus is managed differently than a pure thrombus, further imaging was pursued.

CMR can be valuable in determining whether a mass is a tumor or thrombus by characterizing its size, location, and enhancement pattern. Metastatic tumors generally appear as increased signal on CMR with gadolinium contrast (7). Depending on the vascularity of the tumor and tumor type, the mass will be visualized as increased signal on either T₁ or T₂ imaging. Thrombus, in contrast, manifests as a nonenhancing mass on first-pass perfusion. The mass remains as homogenous nulling (black) on delayed enhancement images even with long inversion times (>500 ms) (7). Post-contrast magnetic resonance images of our patient demonstrated this homogenous nulling.

No clear guidelines exist for management of catheter-associated RA thrombus. A meta-analysis of a similar cohort of patients with dialysis catheter-related atrial thrombi recommended catheter removal when possible (8). Anticoagulation alone for 6 months is recommended for patients with thrombus 6 cm, cardiac adverse events due to the thrombus, or anticoagulation failure, and surgical versus endovascular removal is recommended based on the feasibility of each approach. (8).

Patients with brain metastasis are at high risk for both thrombosis and bleeding (9). Intracranial hemorrhage (ICH) in these patients carries a high mortality rate. Thrombolytics have a 22% reported risk of bleeding, with ICH composing around 3% of such events. Large thrombi can also embolize during lysis (10). Our patient was placed on anticoagulation while determining definitive treatment. Low-molecular-weight heparin, when compared with warfarin, reduces the risk of recurrent VTE in patients with cancer-associated thrombosis and has a lower incidence of nonmajor bleeding (3). There is some evidence that direct oral anticoagulants have equal efficacy as low-molecular-weight heparin at treating cancer-associated VTE, although these therapies may have higher bleeding rates with certain cancer types (3). Importantly, 1 review study found that patients with brain metastasis did not have an increased risk of ICH on anticoagulation, and 1 retrospective study noted possible lower risk of ICH with direct oral anticoagulants compared with enoxaparin (9). Given the encouraging but limited available data, anticoagulation in patients with brain metastasis remains controversial but not unreasonable.

Our patient ultimately underwent endovascular thrombectomy via AngioVac, which employs a modified venovenous extracorporeal bypass circuit to remove a thrombus, with success rate of 73% based on 1 case series (10). Patients must be anticoagulated during this procedure, which can exclude potential candidates. A major safety benefit associated with AngioVac is that it does not lyse the thrombus, so there is a lower risk of embolization during clot removal. Once the thrombus was removed, our patient's symptoms resolved, and he recovered uneventfully. He continues cancer and cardiac surveillance with oncology and cardio-oncology.

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