CLINICAL VIGNETTE

Extensive Deep Vein Thrombosis Undetected by Multiple Modalities in a Patient with Breast Cancer

Zorawar Noor, MD

Case

A 67-year-old woman undergoing neoadjuvant chemotherapy for clinical stage II triple negative left breast cancer presented to clinic with three days of severe swelling, tightness, and purple-blue discoloration of her right upper extremity (RUE), on the same side of her implanted central venous access (port). Past medical, surgical, and family history were unremarkable and she was taking over the counter medications as needed for constipation and nausea. Upon review of systems, she denied loss of sensation, but she noted prominent veins over her right chest for the past day.

Her blood pressure was 120/74, pulse 82 bpm, temperature 36.4°C, respiratory rate of 15 rpm, SpO2 97% on room air, weight 61.4 kg (with a BMI of 21.5 kg/m2). Physical examination was remarkable for severe RUE edema and cyanotic discoloration of the right hand and forearm. The extremity was warm throughout without erythema or rash and sensation was intact. There was venous congestion with significant collateralization of the veins over her neck and right upper chest wall (Urschel's sign). There was no facial plethora, and it was not elicited by raising both her hands above her head (negative Pemberton's sign). The port had no surrounding erythema and was nontender upon palpation. Bilateral breast exam demonstrated good partial clinical response to treatment. Laboratory studies were notable for WBC of 3.1, Hgb 10.7, and Plt 250.

Upper extremity doppler ultrasound (US) was negative for deep vein thrombosis (DVT). A CT venogram (CTV) of the chest and RUE was then performed to look for a DVT or mediastinal mass, and was negative. She was then admitted to an outside hospital and interventional radiology was consulted. Venography by fluoroscopy demonstrated extensive collateralization into the base of the neck, ultimately draining to the external jugular and right brachiocephalic. Subclavian vein occlusion was felt to be from stenosis rather than a DVT. Balloon venoplasty was performed and the port was removed because central venous access was not required for the remaining three doses of weekly paclitaxel chemotherapy. She was discharged to home.

Over the next week, the patient's symptoms continued to worsen with worsening right arm discomfort, swelling, and violaceous discoloration. Repeat doppler ultrasound (US) demonstrated no evidence of DVT, but a nonocclusive superficial thrombosis of the right basilic vein was seen. Despite four imaging studies without evidence of DVT, the clinical suspicion remained high. Therefore, the patient was empirically started on therapeutic dose rivoroxaban at 15 mg BID and an MRI Venogram (MRV) was ordered of the RUE. MRV demonstrated multifocal upper extremity DVT involving the right subclavian, axillary, and brachial veins. The patient underwent successful thrombectomy and removal of a large chronic thrombus and balloon angioplasty of a focal subclavian vein stenosis at the area of the first rib. The patient had rapid improvement within hours of the procedure with complete resolution of her symptoms at one month. The patient underwent surgical resection of her breast cancer and was found to have no residual cancer at the time of surgery. At three months after starting anticoagulation, the patient strongly desired discontinuation of her anticoagulation. The d-dimer was negative, and a repeat MRV was negative, there was no active cancer, so the joint decision was made to discontinue anticoagulation.

Discussion

The subclavian and axillary veins are the most common veins affected in an upper extremity DVT. Seventy to eighty percent of superficial or deep vein thrombi in the upper extremities are due to intravenous catheters.[1,2] The rest are attributed to mechanical or anatomic abnormalities. In this case, the clinical suspicion was high because of the implanted central venous access port, but the general risk of a port associated DVT is relatively low (2-4%).[3,4] In patients with cancer, use of a port rather than a peripherally inserted central catheter (PICC) line is associated with an approximately 60% reduction in risk of catheter associated thrombus.[3]

With severe DVT, there can be increasing venous outflow obstruction and phlegmasia cerulea dolens (PCD), which is defined as severely painful, blue, and inflamed extremity due to a DVT. When she developed signs of early PCD, anticoagulation was started urgently to prevent the potential complications of massive pulmonary embolus (PE), compartment syndrome, or ischemia of the limb due to arterial compromise. While a PE is possible from an upper extremity DVT, the vast majority (96%) of PEs are not attributable to an upper extremity DVT.

Diagnosis is usually made by Doppler US with compression, which has a sensitivity of 91% and specificity of 93% for upper

extremity DVT.[5] One drawback of US is that direct visualization of the proximal subclavian vein can be difficult due to shadowing from the clavicle.[6] CT or MRI can be useful, but they must be sequenced for the venous phase for highest sensitivity. A pooled analysis looking at the accuracy of MRI for suspected DVT estimated pooled sensitivity of 91.5% and specificity of 94.8%, with an approximately 30% higher sensitivity for proximal rather than distal DVTs.[7]

This case demonstrates that the cornerstone for diagnosis of a DVT still rests upon history and clinical diagnosis. To help, clinical probability scores like the "Wells score " and "modified Wells score" were created and are widely used in clinical practice. In this case, clinical judgment was used for empiric anticoagulation and the risk of bleeding had to be weighed carefully. Even though bleeding scores like "HAS-BLED," "ATRIA," "OBRI," and "HEMORR2HAGES" exist, they are far less useful because they generally do not perform better than clinical judgment.[8] Therefore, the decision for empiric anticoagulation and in a high-risk patient still relies upon clinical decision-making.

There is no universally accepted optimal duration of anticoagulation for a first DVT (3 months, 6 months, or 1 year), but general agreement is that a minimum of 3 months of anticoagulation is necessary. If the central venous catheter is not removed, some guidelines states that anticoagulation should continue until 3 months after removal.[9] In patients with active cancer or recurrence on anticoagulation, consideration should be given for longer than the usual 3-6 months for an initial DVT.

Large randomized controlled trials and meta-analyses have demonstrated that low molecular weight heparin (LMWH) has superior efficacy to warfarin in the treatment of DVT for patients with active cancer. Therefore, LMWHs remained the standard of care until more recent studies demonstrated the efficacy of direct oral anticoagulants (DOACs). Three randomized trials have demonstrated similar, if not better efficacy of a DOAC when comparing dalteparin with endoxaban (Hokusai VTE Cancer Investigators),[10] rivaroxaban (SELECT-D),[11] and apixaban (CARAVAGGIO).[12] DOACs are now listed along with LMWH as first-line treatment by the American Society of Cancer Oncologists and National Comprehensive Cancer Network guidelines.[13,14] One should note that these trials excluded or limited high risk patients with a history of bleeding, thrombocytopenia, primary and metastatic brain lesions, hematologic malignancies, or upper GI malignancies. DOACs are sometimes thought of as interchangeable, but there are key notable differences to be considered, including the possible need for LMWH bridging prior to DOAC, different renal and liver metabolism, and available US Food and Drug Administration (FDA) approved reversal agents.

In summary, high clinical suspicion should guide empiric anticoagulation for DVT and additional evaluation. MRV and venogram should be considered for a suspected upper extremity DVT if other modalities fail. DOAC should be considered in a patient with active cancer and DVT. The optimal duration of anticoagulation is unclear, but at least 3 months is recommended.

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