WHAT WOULD YOU DO?

Acute Thrombus of the Inferior Vena Cava Extending to the Femoral Veins

MODERATORS: IDO WEINBERG, MD, AND ROBERT M. SCHAINFELD, DO, FSVM, FSCAI

PANEL: ANNEMARIE E. FOGERTY, MD; ROBERT M. SCHAINFELD, DO, FSVM, FSCAI; AND MITCHELL D. WEINBERG, MD, MBA

CASE PRESENTATION

A 61-year-old woman underwent laparoscopic cholecystectomy for acute cholecystitis. During this procedure, a right upper pole renal mass was incidentally noted, measuring 9.2 cm at its maximum dimension (Figure 1).

Six weeks later, the patient underwent right radical nephrectomy and suprarenal inferior vena cava (IVC) surgical thrombectomy. The pathological specimen retrieved during this procedure revealed clear cell renal cell carcinoma (RCC; Fuhrman grade 3) invading the renal vein and sinus fat. All 25 sampled lymph nodes were negative for malignancy.

Postoperatively, she received intravenous unfractionated heparin and was subsequently discharged home on enoxaparin 40 mg once daily.

How long would you administer low-molecular-weight heparin, either a prophylactic or therapeutic dose, postoperatively?

Dr. Fogerty: The first principle in determining whether anticoagulation is indicated is to differentiate tumor thrombus from traditional thrombus, which is often classified as bland thrombus. A tumor thrombus is not expected to respond to anticoagulation, whereas anticoagulation is the appropriate treatment for traditional or bland thrombi. Intravascular tumor thrombus is defined as tumor extension directly into a vessel. Its presence has implications for oncologic management because

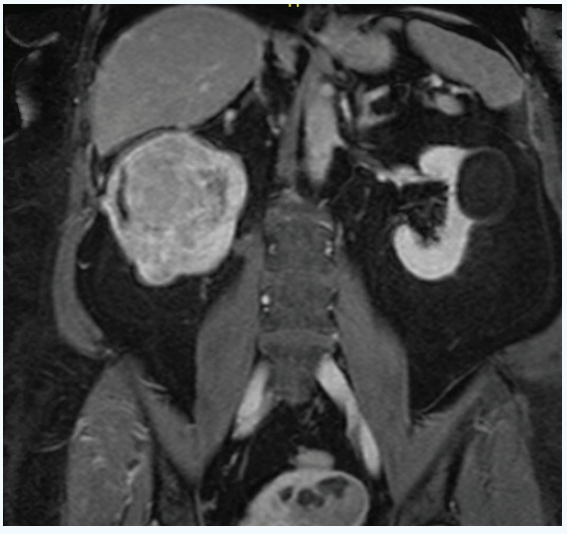

Figure 1. Coronal magnetic resonance T1 image of the abdomen and pelvis with contrast revealing a right kidney mass. Note there is also a left kidney cyst.

it impacts the stage, prognosis, and treatment. Tumor thrombosis can occur in any malignancy, but is most frequently associated with RCC, Wilms tumor, adrenocortical carcinoma, and hepatocellular carcinoma.

Radiographic features are the mainstay in differentiating tumor from bland thrombosis. A tumor thrombus will directly invade and extend into the vessel contiguous with the malignant mass, is expected to show enhancement, and will uptake fluorodeoxyglucose on positron emission tomography.[1] Venography will show a filling defect within the affected vessel in both tumor and bland thrombus.

As described, this case is most consistent with tumor thrombus. As such, systemic anticoagulation would not be indicated. It is important to remain vigilant for evidence of thrombosis in this patient and pursue limb duplex ultrasounds to assess for deep vein thrombosis (DVT) if asymmetric leg pain or edema develop. Prophylactic enoxaparin is not unreasonable given this patient would be defined as hypercoagulable due to primary malignancy, the recent postoperative state, and expected decreased mobility given postoperative recovery. The prescribed course of prophylaxis would depend on recovery to the prior baseline functional state of ambulation and hydration, which is typically 2 weeks after surgery.

Dr. Schainfeld: The differential diagnosis as to the etiology of the acute venous thrombosis involving the IVC, iliac veins, common femoral vein (CFV), femoral/popliteal, and calf veins implies an extensive degree of clot burden. There are a number of independent and cumulative risk factors at play to explain the acute DVT.

First, the patient has a recently confirmed malignancy, specifically clear cell RCC, which implicates that the patient is in a prothrombotic state. Superimposed is the "behavior" of the tumor, which in this case, had already invaded the renal vein and adjacent IVC at the time of the initial diagnosis, which was confirmed at the time of surgical exploration. Furthermore, additional risk factors for the development of DVT is compounded by a recent laparoscopic surgical procedure and subsequent open operation entailing radical nephrectomy and adjunctive surgical venous thrombectomy. In addition, her advanced age and bed rest, in the context of the aforementioned malignancy and complex surgical procedures, would stratify this patient into a high-risk category for DVT/pulmonary embolism.

CASE CONTINUED

At postoperative day 25, the patient presented with right calf swelling and associated pain of 2 days' duration. As the swelling progressed to also involve her thigh, she presented to the emergency department. Venous duplex ultrasonography revealed acute thrombus involving the CFV extending caudal to the calf veins (Figure 2).

What are potential causes for the lower extremity venous and IVC thrombus?

Dr. Mitchell Weinberg: The history of laparoscopic cholecystectomy is notable but not terribly concerning. The incidence of symptomatic DVT after laparoscopic cholecystectomy was low (0.4%) in an analysis from the Nationwide Inpatient Sample.[2] Additionally, given the considerable hiatus after the initial cholecystectomy, this surgery is unlikely to have markedly amplified the patient's DVT risk. In stark contrast, open nephrectomy was a likely contributor. The average postoperative DVT risk after nephrectomy is roughly 1%. An open surgical approach, large tumor burden, the presence of distant metastases, and longer operating room times have been cited as risk-enhancing features.[3]

Dr. Fogerty: Virchow's triad refers to abnormalities of three key areas that contribute to thrombus formation and propagation: stasis of blood flow, endothelial injury, and hypercoagulability. Cancer patients are at increased risk for thrombosis, as both malignancy and its treatment can introduce abnormalities to all three areas. Stasis and endothelial injury can result from surgery, tumor encasement of blood vessels, hemodynamic compromise, or a bedridden state due to surgery or general

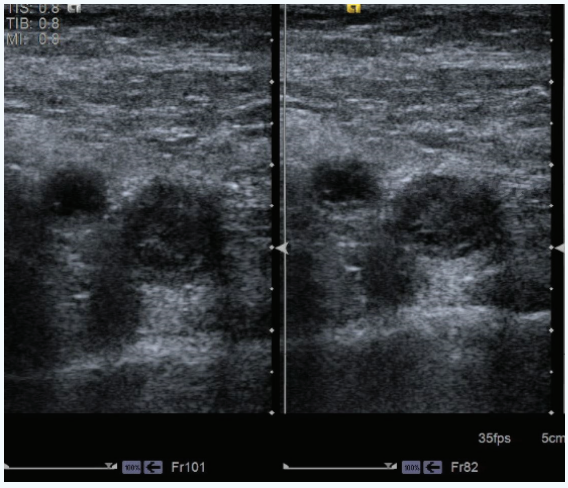

Figure 2. Duplex ultrasound images of the right CFV with and without compression. Lack of compressibility is consistent with a right CFV thrombus.

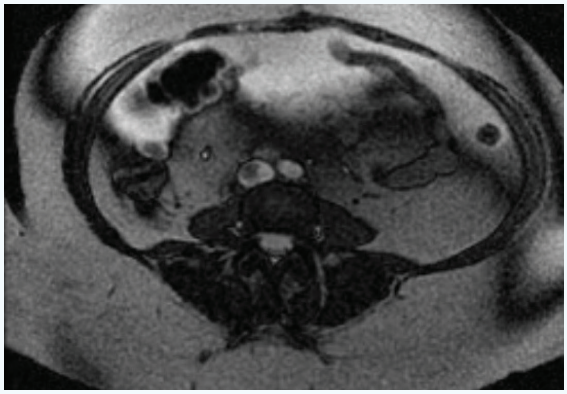

Figure 3. Axial MRV revealing nonocclusive thrombus within the IVC.

illness. The hypercoagulability of cancer also involves the ability of tumor cells to produce and secrete procoagulant/fibrinolytic substances and inflammatory cytokines, as well as the physical interaction between tumor cell and blood or vascular cells. In this case, recent surgery with direct manipulation of the IVC would contribute to venous stasis and endothelial injury. The continued exposure to heparin would also raise concern for heparin-induced thrombocytopenia with thrombosis (HIT/HITT), which would serve as an additional risk within the hypercoagulable category of Virchow's triad.

Although thrombocytopenia is a fairly common complication of cancer and its treatment, HIT is not more likely to occur in cancer patients than in the general population. Typically, the thrombocytopenia occurring in a cancer patient undergoing active treatment would be due to bone marrow suppression of chemotherapeutics, bone marrow invasion of cancer, or thrombopoietin deficiency in the case of liver cancer or metastases. In such cases, bleeding is the primary concern. In this case, however, there is no mention of chemotherapy or other new medications that may have resulted in bone marrow suppression. The decrease in platelet count of > 50% during exposure to heparin in a patient with newly diagnosed DVT appropriately prompts assessment for the pathophysiologic PF4 antibody. A positive finding would define HITT, for which systemic anticoagulation with a nonheparin agent is indicated. The thrombocytopenia of HIT is not considered a bleeding risk factor, but paradoxically represents increased thrombotic risk due to the underlying pathophysiology.

CASE CONTINUED

Because the thrombus extended into the CFV, magnetic resonance venography (MRV) was performed, which revealed that the clot extended through the iliac veins and into the IVC (Figure 3). Table 1 shows the patient's blood count on postoperative days 7 and 25.

HIT was suspected. Laboratory testing was performed for antiplatelet factor 4 antibodies and serotonin release assay, and both returned positive for HIT.

Should this patient be offered a procedure in the post-ATTRACT trial era? What is this patient's risk regarding catheter-based clot removal? Does the presence of HITT increase bleeding risk?

Dr. Schainfeld: In the ATTRACT trial, major bleeding within 10 days occurred in 1.7% of patients assigned to the pharmacomechanical thrombolysis group as compared to 0.3% assigned to the control group (P = .049).[4] In the context of this patient, because she had several active exclusion criteria that would disqualify her candidacy for ATTRACT, it would be difficult to discern her risk for bleeding, although one could justify that it would be considerably higher than articulated in the results of the ATTRACT trial. Notably, the patient would not qualify for the ATTRACT trial due to the presence of HIT and active cancer. Also, the presence of HIT would certainly confound the natural history of her disease if a decision were made to proceed with an invasive endovenous intervention employing thrombolytic agents.

Dr. Mitchell Weinberg: The decision to offer thrombectomy is based on patient symptoms and assessed bleed risk. The pre- and post-ATTRACT era are identical when it comes to the management of proximal iliofemoral vein DVT. Highly symptomatic patients should be offered treatment. Unfortunately, ATTRACT did not isolate such patients well; however, there was a suggestion of benefit in this cohort of patients with more proximal DVT. We quote an intracranial hemorrhage (ICH) risk of 0.5% to 2% in patients undergoing

TABLE 1. RESULTS OF BLOOD TESTING FOR CASE PATIENT

	White Blood Cell Count	Hematocrit	Platelet Count
Discharge (postoperative day 7)	4,560/µL	24.4%	277 X 10^3/µL
Emergency department presentation (postoperative day 25)	12,200/µL	22.2%	45 X 10^3/µL

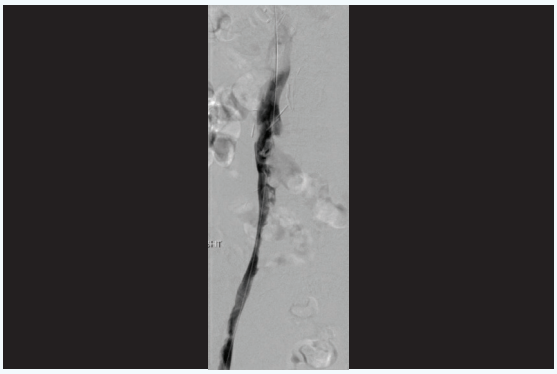

Figure 4. Contrast venography post-CDT the following day, before rheolytic thrombectomy and balloon venoplasty of the CFV and iliac veins. Injection was performed via right popliteal venous sheath. Findings of note include patent popliteal, femoral, CFV, and iliac veins and infrarenal IVC, although there is residual thrombus involving the CFV and particularly the iliac veins. Surgical clips adjacent to the IVC are consistent with previous nephrectomy.

catheter-directed lysis. Assessment of major bleeding risk outside of ICH must be adapted to the specific patient. We would consult with the patient's uro-oncologists to more accurately understand the postsurgical bleeding risk in this particular patient.

The venogram is notable for a modest venous stenosis in the mid-common iliac vein. Although this could represent a filling defect from residual thrombus burden, extrinsic compression is worth considering. As the patient's DVT occurred on the right side, an atypical pattern of iliac vein compression should be contemplated. Atypical patterns of iliac vein compression account for 2.2% of reported cases in the literature. More than half of these atypical cases are isolated right-sided iliac vein compression (1.4% of literature reported cases).[4] The two most common clinical features that have been noted in patients with iliac vein compression who present with DVT are recent surgery (16.9%) and a history of malignancy (11.2%)—both clinical features possessed by this patient.[5]

Certainly, the hypercoagulability associated with the renal cancer, the postoperative state, and the venous stasis associated with right-sided iliac vein compression could explain the extensive right-sided DVT this patient experienced. More interestingly, patients with iliac vein compression are theoretically more dependent on collateralized venous outflow from the gonadal vein. Radical nephrectomy, which by definition includes gonadal vein ligation, may have created profound venous stasis in this patient by compromising a vital venous conduit, rapidly overwhelming the flow capacity of the already compressed iliac vein.

CASE CONTINUED

After considerable discussion among all providers and the patient as to the benefits and attendant risks of the proposed procedure, she consented to proceed with the endovenous interventional procedure.

Details of the procedure included obtaining right popliteal vein access with ultrasound guidance with the patient in prone position. Digital contrast venography from the popliteal vein to the IVC was performed. Findings were significant for acute thrombus of the popliteal (nonocclusive), femoral, CFV, and external and common iliac veins and proximal extension up to juxtarenal IVC (Figure 4).

Please discuss two or three technical aspects you feel are important in procedures of this type.

Dr. Mitchell Weinberg: Popliteal access requires prone positioning and creates some challenges with periprocedural sedation and patient comfort. The patient must tolerate resting on her abdomen for over an hour. There are a variety of approaches for radical nephrectomy, but some involve more anterior approaches. If this patient has abdominal incisions or existing drains and tubes, they could impair the patient's ability to tolerate the procedure.

Accessing this patient's occluded popliteal vein will likely be easily achieved with ultrasound-guided access, because the clot is likely still quite fresh and should be easily penetrated with a puncture needle and wire. Many operators use larger-bore needles to puncture the vein. However, as there is no venous flow back into the needle during venipuncture of a totally thrombosed vein, we prefer to use an echogenic micropuncture needle. This offers both sonographic visualization and excellent tactile feedback to the operator, which facilitates easy positioning of the needle tip in the center of the popliteal vein. Once the micropuncture sheath is in place, we advance an angled-tip Glidewire (Terumo Interventional Systems) to at least the CFV. We prefer Brite Tip sheaths (Cordis, a Cardinal Health company) so that we can accurately withdraw the bulk of the sheath, leaving only its tip in place. This allows for safe treatment of the more distal segments of the popliteal vein without accidental withdrawal of the sheath from the vein.

Once the decision to intervene is made, the treating physician may choose from a wide variety of treatment strategies and endovascular devices. Catheter-directed lysis is the simplest endovascular option available and

is preferred by many. However, in very symptomatic patients with proximal DVT, we prefer mechanical and rheolytic thrombectomy because of the rapid clot dissolution and early symptom relief they provide. The AngioJet ZelanteDVT catheter (Boston Scientific Corporation) can be inserted through a 9-F sheath via the popliteal vein. Over the course of a few minutes, 10 to 20 mg of alteplase diluted in 100 mL of normal saline is disseminated throughout the thrombus. The ZelanteDVT catheter tip can be rotated by the operator to direct the alteplase to the region of interest. In the presence of large iliac vein thrombus, we rotate the catheter 90° with each 1-cm advance to maximize the volume of thrombus exposed to the lytic agent.

Once all the alteplase is administered during the pulse phase, most practitioners wait 25 minutes to allow the alteplase to marinate. Thereafter, the same ZelanteDVT catheter system is used to perform rheolytic thrombectomy after the necessary adjustments are made on the device console. We aim to keep the cumulative thrombectomy time to < 8 minutes and limit the total thrombectomy volume to < 1 L. When treating proximal DVT, such as in this case, we hydrate aggressively throughout the procedure to reduce the risk for nephropathy associated with myoglobinuria.

Although pulse lysis with rheolytic thrombectomy is often sufficient, additional therapy is occasionally needed afterward. Extensive residual thrombus or persistent thrombosis of the iliac veins and/or the profunda femoral vein often prompt the consideration of additional therapies after initial thrombectomy. Some clinicians will perform balloon angioplasty or further mechanical thrombectomy at this point. However, we prefer to place an infusion catheter and administer catheter-directed thrombolysis. Typically, we infuse lytics over an 8- to 12-hour period with 1 mg of alteplase per hour for 4 to 5 hours, followed by 0.5 mg per hour for another 8 hours. Ideally, we prefer to keep the total alteplase dose infused under 25 mg. However, as there are no clear recommendations for the infusion rate and the total infusion time, we tailor our infusion rate and duration to the quantity of residual thrombus and the patient's overall risk for bleeding. For example, in this particular case, the patient's recent surgery would prompt us to minimize the cumulative lytic dose. We would consider an early relook venography after 6 hours of lytic infusion to assess clinical progress and verify the need for further lytic infusion.

Because of the paucity of data demonstrating any significant advantage of Ekos therapy (Ekos Corporation, a BTG International group company) compared to standard infusion catheters, we avoid Ekos and the additional cost that device incurs unless it is part of an ongoing trial protocol.

Dr. Schainfeld: To optimize the technical and clinical success of any vascular intervention, meticulous preoperative planning is imperative and adherence to detail further facilitates eventual success of the procedure. One nuance in this case that is paramount revolves around the potential risk of bleeding given the recent surgical operation. It dictates judicious use of any thrombolytic agent if mandated, thus limiting the total dose administered, duration of infusion, agent, and dose used as an adjunctive anticoagulant in light of HIT, and target goal of partial thromboplastin time (PTT) commensurate with anticoagulant chosen during lytic infusion. Given that the patient was positive for HIT, we used argatroban as our adjunctive anticoagulant of choice, targeting a PTT between 40 and 50 seconds during the recombinant tissue plasminogen activator infusion.

CASE CONTINUED

Tissue plasminogen activator via a 50-cm infusion catheter was administered at 1 mg per hour over the ensuing 16 hours. The next morning, venography demonstrated marked improvement in flow, with residual thrombus in CFV, iliac veins, and IVC with adherent clot at the site of the surgical anastomosis. Therefore, adjunctive use of mechanical thrombectomy with an AngioJet device was employed to attempt to clear residual thrombus. Balloon maceration with percutaneous transluminal balloon venoplasty was performed next and was successful to render the CFV, iliac veins, and IVC patent. A venous stent was deemed not indicated given that at least 90% of thrombus removal with restoration of flow was achieved. A venous stent was deemed not indicated.

The patient tolerated the procedure without incident and was eventually discharged on warfarin with a targeted international normalized ratio of 2 to 3.

How would you follow this patient long term?

Dr. Fogerty: The primary factor that determines the recommended anticoagulation course is whether a thrombosis is classified as provoked versus unprovoked. Provoked thromboses are managed with finite courses of anticoagulation, provided that the provoking risk is resolved. Provoking risk factors include estrogen exposure, pregnancy, surgery, medical immobility, malignancy—and, as in this case, heparin exposure if HIT is diagnosed. Unprovoked thromboses are typically managed with long-term, if not indefinite, anticoagulation because there is no identified risk to modify. Thus, recurrent thrombosis is deemed unacceptably high if anticoagulation is interrupted, averaging about 20% over 2 years.

In this case, the patient was managed for HITT. This is classified as a provoked event, for which the treatment includes immediate discontinuation of heparin and a finite course of nonheparin anticoagulation (typically 3–6 months). If the thrombosis had been attributed to the hypercoagulability of malignancy alone, the anticoagulation duration would depend on the status of the cancer. For cancer-associated thromboses, anticoagulation is continued throughout active treatment for malignancy and while there is any evidence for disease on surveillance. In such cases, typically after 3 to 6 months of therapeutic anticoagulation for an acute event, the anticoagulation intensity can be reduced to prophylactic range.

Dr. Schainfeld: Regarding this patient, it is imperative to ensure longitudinal follow-up, both clinical and objective, following a complex venous intervention, in light of her known active malignancy and venous thromboembolic event/acute DVT. As such, a comprehensive history and physical examination should be performed at regular intervals, such as at 1 to 3 months and at 6 and 12 months for the first year. Complementary imaging should be enforced with venous duplex ultrasound of the right limb and abdomen/pelvis. If clinically driven or if there is any suggestion of acute venous rethrombosis, cross-sectional imaging, specifically CT venography (CTV) should be expeditiously performed to ensure patency of the deep venous system. Because an endovenous stent was not required, although extensive venoplasty was warranted to render veins patent, adjunctive solo antiplatelet therapy, such as aspirin in concert with anticoagulation might be an appropriate pharmacologic regimen postintervention.

Dr. Mitchell Weinberg: In patients undergoing venous intervention for proximal DVT, we routinely obtain a new baseline venous duplex prior to discharge. The study characterizes residual clot burden and the presence of venous respirophasicity, a surrogate for more proximal iliac vein and IVC patency. Patients then return at 1 month for clinical follow-up and a repeat venous duplex. Thereafter, we refrain from further imaging unless the patient notes a new symptom or physical examination demonstrates new evidence of venous obstruction. We do, however, perform repeat venous duplex ultrasonography when the patient concludes anticoagulation in anticipation of DVT recurrence in a small portion of the population.

CASE SUMMARY

At the 3-month follow-up visit, venous duplex ultrasound and CTV of the abdomen/pelvis demonstrated patent femoral, popliteal, and iliac veins as well as IVC with no residual thrombus.

During long-term follow-up at the hematology clinic, the patient's anticoagulation was transitioned to apixaban 5 mg twice daily. Of note, during follow-up, the patient demonstrated a persistently elevated D-dimer level.

At 18 months after nephrectomy, the patient was doing well. She was removed from anticoagulation and is considered disease free. ■

1. Quencer KB, Friedman T, Sheth R, Oklu R. Tumor thrombus: incidence, imaging, prognosis and treatment. Cardiovasc Diagn Ther. 2017;7(suppl 3):S165-S177.
2. Stein PD, Matta F, Sabra MJ. Pulmonary embolism and deep vein thrombosis following laparoscopic cholecystectomy. Clin Appl Thromb Hemost. 2014;20:233-237.
3. Pettus JA, Eggener SE, Shabsigh A, et al. Perioperative clinical thromboembolic events after radical or partial nephrectomy. Urology. 2006;68:988-992.
4. Vedantham S, Goldhaber SZ, Julian JA, et al; ATTRACT trial investigators. Pharmacomechanical catheter-directed thrombolysis for deep vein thrombosis. N Engl J Med. 2017;377:2240-2252.
5. Kaltenmeier CT, Erben Y, Indes J, et al. Systematic review of May-Thurner syndrome with emphasis on gender differences. J Vasc Surg Venous Lymphat Disord. 2018;6:399-407.

Ido Weinberg, MD
Assistant Professor of Medicine
Harvard Medical School
Vascular Medicine Specialist
Massachusetts General Hospital
Boston, Massachusetts
iweinberg@partners.org
Disclosures: Scientific advisory board for Novate Medical.

Robert M. Schainfeld, DO, FSVM, FSCAI
Associate Director, Vascular Medicine
Massachusetts General Hospital
Boston, Massachusetts
rschainfeld@mgh.harvard.edu
Disclosures: None.

Annemarie E. Fogerty, MD
Center for Hematology
Massachusetts General Hospital
Boston, Massachusetts
afogerty@partners.org
Disclosures: None.

Mitchell D. Weinberg, MD, MBA
Northwell Health System
Zucker School of Medicine at Hofstra University
Hempstead, New York
mweinberg4@northwell.edu
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