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Peri-operative Management of Heparin-Induced Thrombocytopenia Syndrome in a Patient With a Suspected Gynecologic Malignancy

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Seminars in Oncology

At times we encounter clinical problems for which there are no directly applicable evidence-based solutions, but we are compelled by circumstances to act. When doing so we rely on related evidence, general principles of best medical practice, and our experience. Each "Current Clinical Practice" feature article in *Seminars in Oncology* describes such a challenging presentation and offers treatment approaches from selected specialists. We invite readers' comments and questions, which, with your approval, will be published in subsequent issues of the Journal. It is hoped that sharing our views and experiences will better inform our management decisions when we next encounter similar challenging patients. Please send your comments on the articles, your challenging cases, and your treatment successes to me at dr.gjmorris@gmail.com. I look forward to a lively discussion.

Gloria J. Morris, MD, PhD
Current Clinical Practice Feature Editor

Thromboembolic disease represents the second leading cause of morbidity and mortality among patients with malignancy.[1,2] For patients with acute thromboembolic disease who are hemodynamically stable, initial treatment with low-molecular-weight subcutaneous heparin is recommended secondary to their high bioavailability, longer half-life, and decreased variation in the anticoagulant response.[3]

Approximately one in three hospitalized patients are exposed to heparin.[4] Heparin-induced thrombocytopenia (HIT) is a serious potential side effect in patients receiving heparin therapy. While the absolute incidence is low, close to 0.2% of patients receiving unfractionated heparin, the morbidity and mortality risks are significant. These include approximately a 20% mortality rate and a 10% major morbidity rate. Thrombotic events are fatal in 21% of patients with HIT.[4]

HIT should be suspected clinically in patients whose platelet counts decreases by 50% and/or who have thrombosis 5–14 days after starting heparin therapy.[5] HIT is caused by antibodies that attack the heparin/plate factor 4-antigen complex on platelets; upon activating them, they cause the release of pro-coagulant and vasoconstrictive substances.[6] This can result in limb-threatening venous clots and life-threatening pulmonary emboli.

HIT is usually verified with laboratory studies, including the serotonin release assay (SRA), heparin-induced platelet aggregation assay (HIPA), or heparin–platelet factor 4 (H-PF4) enzyme-linked immunosorbent assay (ELISA). The combined use of two or more of these tests improves the sensitivity and specificity of the HIT diagnosis.[7] Once HIT is diagnosed, heparin should be discontinued and alternative anticoagulation therapy should be initiated. Direct thrombin inhibitors such as lepirudin, argatroban, and bivalirudin are acceptable alternatives.[8]

Argatroban, derived from L-arginine, is the only anticoagulant approved for both interventional and non-interventional settings for patients diagnosed with HIT. Argatroban is hepatically metabolized and can be administered safely in patients with renal disease.[9] For long-term anticoagulation in patients with HIT, argatroban can be transitioned to warfarin therapy once platelets have reached at least 150,000/μL.[8] There should be at least 5 days of combination argatroban-warfarin therapy with a goal international normalized ratio (INR) of 2.0–3.0 before argatroban is discontinued.[8] Warfarin therapy should be continued for at least 2–3 months in HIT patients who do not experience a thrombolic event, at least 3–6 months in patients with HIT and a thrombolic event, and potentially extended further in patients with a malignancy.[7]

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While perioperative management of warfarin and heparin varieties are well understood, much less is known about the perioperative management of argatroban. We present a case of a patient with recently diagnosed HIT requiring emergent surgery for a suspicious gynecologic mass. The recommendations of a multidisciplinary team.

CASE REPORT

A 56-year-old nulliparous (G0) white female presented to the emergency department with painful swelling of the left lower extremity extending from the calf upwards into the thigh. A duplex ultrasound revealed a deep venous thrombosis (DVT) that extended from the left popliteal vein to the common femoral vein. Although not dyspneic, a computed tomography (CT) scans of the chest, abdomen, and pelvis done for systemic evaluation demonstrated bilateral pulmonary emboli, and additionally detected a large heterogeneous cystic mass with solid components in the pelvis that measured 13.7 × 10.9 × 11 cm in size with mild left hydronephrosis. The patient was admitted to the hospital to a general medicine service, was started on intravenous heparin for anticoagulation, and the gynecologic oncology service was consulted. Two days into her hospital course, she underwent placement of a Greenfield filter in preparation for surgical removal of the pelvic mass, slated ideally in 10–14 days hence. She was discharged to home on enoxaparin 80 mg subcutaneously twice daily for anticoagulation. Her platelet count during the admission was recorded at 225K/μL (normal range 140–400K/μL), and remained stable until discharge.

The patient's past medical history is significant for right breast cancer in 2006 and chronic sinus infections. Her surgical history includes a partial mastectomy of the right breast in 2006, reconstruction of her right ankle, appendectomy, and tonsillectomy. The family history is remarkable for breast cancer in her mother and her maternal and paternal grandmothers. In addition, her family history is relevant for numerous accounts of thrombi in her mother, sister, and maternal uncle. The patient describes herself as a social consumer of alcohol with a 40-pack year history of tobacco abuse.

Medications prior to this admission included a seasonal allergy drug as needed and allergy injections every 3 weeks. She had an extensive history of anaphylactic reactions to antibiotics, including penicillins, cephalosporins, sulfa drugs, and levofloxacin. Due to her extensive history of antibiotic sensitivities, the patient was scheduled to be readmitted to the hospital prior to the surgical removal of the pelvic mass for desensitization to antibiotics.

Upon readmission, however, her platelet count had decreased to 79K/μL. The patient was suspected of experiencing HIT and her blood was examined for heparin-associated platelet antibodies with an ELISA test. Antibodies to the H-PF4 complex were discovered and HIT was confirmed with a positive SRA test. Enoxaparin was discontinued, the patient was started on argatroban, and surgery was postponed.

Three days later, the patient complained of dyspnea with abdominal discomfort. Repeat CT scan revealed new onset ascites with a growth of the pelvic mass to 17 × 12 cm. The scan also demonstrated a continued left lower extremity venous thrombosis with diminishing bilateral pulmonary emboli. Her platelet count was 183K/μL. Subsequently, her creatinine levels had elevated from 0.6 to 1.1 over the previous 8 days. It was suspected that the enlarging mass was causing acute renal insufficiency secondary to ureteral obstruction and the decision was made to surgically remove the mass. Argatroban was discontinued 4 hours prior to surgery and the patient underwent exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, tumor debulking, extensive dissection of the left retroperitoneal space, and tumor staging. Argatroban was restarted on postoperative day 2 and the medical team arranged for the patient to begin outpatient chemotherapy treatment with bleomycin, etoposide, and cisplatin based on a final pathology report revealing a stage IIIC left ovarian primitive neuro-ectodermal tumor arising in the background of a grade 3 endometroid carcinoma (Figure). However, when the patient began chemotherapy 1 month later, CT imaging revealed progression of her disease, including multiple new pelvic masses of which the largest measured 8 × 5 cm in size and suspected pulmonary lesions suspicious for metastasis. At this time, the patient declined further chemotherapy treatment.

We posed the following clinical questions: (1) What would you recommend for the preoperative management of a patient with a recent history of a DVT and/or pulmonary embolism (PE)? (2) How do you recommend managing argatroban in a patient with HIT when surgery is advisable? (3) How would you manage this primitive neuroectodermal tumor postoperatively?.

Hematologist's Expert Opinion

This case brings up a few relevant issues. The challenges in this case include surgery in the setting of recent thrombosis, thrombosis in the setting of malignancy, as well as postoperative management of alternative anticoagulation in a high-risk patient. Generally, in the

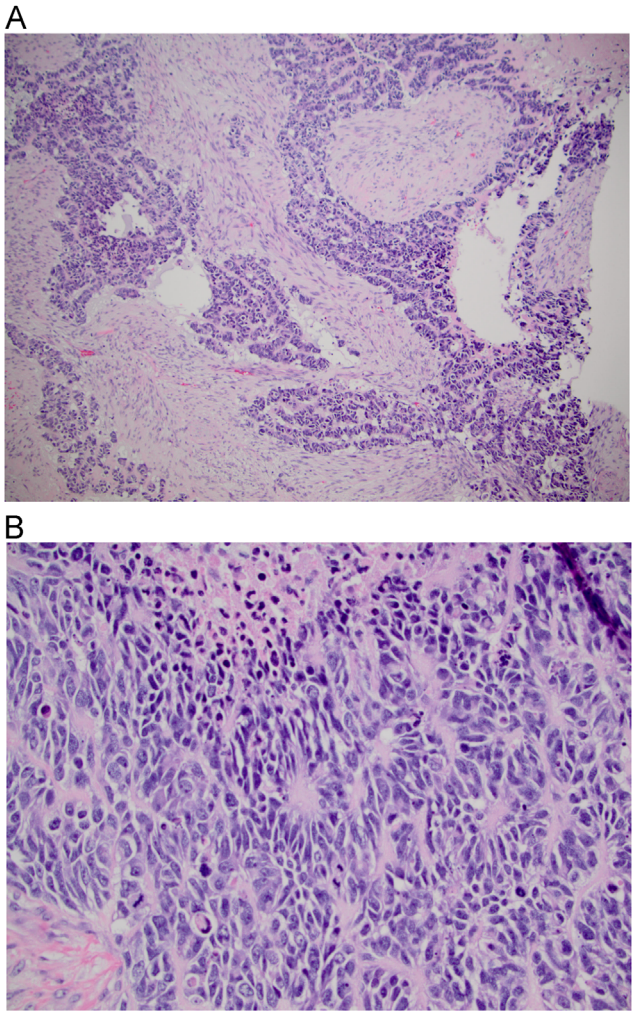

Figure. Primitive neuroectodermal tumor arising in an endometrioid carcinoma. The primary site for this neoplasm was the 13 x 8 x 7.5 cm left ovary, which on section (A) reveals a partly cystic, partly solid appearance. Multiple metastases were identified in the pelvis and abdomen. Histologically, the scant endometrioid component of the tumor is composed of malignant glands that express cytokeratin 7, vimentin, estrogen receptor and PAX8. (B) The majority of the tumor is represented by the primitive neuroectodermal component. These areas are composed of small cells with scant cytoplasm arranged in sheets, cords and rosettes (Figure 2). Mitoses are abundant, and necrosis is present. Immunohistochemical evaluation reveals expression of vimentin, CD56 and Fli-1, while epithelial markers (Cam 5.2, AE1/AE3, cytokeratin 7, epithelial membrane antigen), GFAP, neurofilament, inhibin and desmin are negative. CD99 immunostain shows a perinuclear dot-like pattern of positivity. Courtesy of Dr. Elizabeth Dellers, LeHigh Valley Health Network, Department of Pathology, Allentown, PA.

setting of recent thrombosis, guidelines recommend that elective surgery should be avoided. During the first month after a thrombosis, there is a 1% absolute increase in the risk of recurrence each day without anticoagulation. In this situation, surgery could not be delayed; however, even a 2-week delay decreases the risk of further thrombosis.

In the setting of HIT, inferior vena cava filter placement should be avoided as the risk of venous thromboembolism is very high, and filter placement serves as nidus for thrombosis. What is interesting in this case is that she did not develop her initial thrombosis in the setting of platelet activation due to HIT, but that HIT developed during her treatment for thrombosis. However, regardless of the initial reason for initiation of heparin therapy, risk of further thrombosis remains. The incidence of HIT in the setting of malignancy has been found to be increased compared to the general population. Prandoni et al have reported the incidence of HIT to be 1.5% in cancer patients as opposed to 0.7% in patients without cancer, and higher thrombotic rates in cancer patients with HIT have been reported.[9] Patients are considered less prothrombic when the platelet count has improved, and ideally surgery is delayed until the antibody has cleared.

As a hematologist, the goal is to find the balance between thrombotic risk and bleeding risk in each patient. However, in the surgical setting this cannot be performed in a vacuum and understanding the surgical risk of bleeding, which can vary based on the procedure, is crucial. In settings such as these, the timing of discontinuation of anticoagulant therapy should be based on the half-life of the drug and bleeding risk associated with the surgery. We extrapolate from recommendations regarding intravenous heparin use when alternative anticoagulants are used. The elimination half-life of heparin ranges from 30–120 minutes. Thus, guidelines advise that unfractionated heparin should be stopped 4 hours before surgery. Given this, we generally advise withholding argatroban for 2 hours, based on its half-life of 40–51 minutes, with partial thromboplastin time (PTT) evaluation to ensure normalization prior to proceeding.

Determining when to restart anticoagulation often requires input of the surgeon to understand bleeding risk if anticoagulation is started too early and input of the hematologist to try to determine

thrombotic risk during the anticoagulant-free window. The closer to surgery anticoagulation is started, the higher the bleeding risk. Bleeding risk is considered highest when anticoagulation is given 8 hours postoperatively and lowest when given 24 hours postoperatively. In this patient with high thrombotic risk, restarting anticoagulation 12–18 hours postoperatively, assuming adequate hemostasis was achieved is reasonable.

In this type of situation, each patient must be viewed independently, with their various risk factors taken into account. Multidisciplinary communication and management is vital to success.

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Gynecologic Oncologist's Expert Opinion

Armand Trousseau initially described in 1865 the syndrome of unexplained, migratory thromboses that precede or appear concomitantly with diagnosis of visceral malignancy.[10] In a retrospective review of 654 patients undergoing exploratory laparotomy for gynecologic malignancy, 25 (3.4%) patients were found to have preoperative DVT.[11] Among patients undergoing surgery for ovarian cancer, the incidence of preoperative DVT has been estimated to be 6%–25%[11,12] and DVT with PE, 11.1%.[10] The preferred treatment is heparin or low molecular weight heparin (LMWH), with vitamin K antagonists being relatively inactive.[13]

There is limited information available to guide the clinician in the management of pre-operative thromboembolic disease. The American College of Chest Physicians evidence-based guidelines for the perioperative management of antithrombotic therapy, 9th edition, provides no recommendation regarding this issue.[14] Orr et al recommend that surgery be delayed at least 4 weeks after the diagnosis thromboembolic disease.[15]

Shiozaki et al described their management of 25 patients undergoing laparotomy for gynecologic malignancy who were diagnosed preoperatively with DVT.[11] Three patients with only a small, organized thrombus were treated with standard venous thromboembolism (VTE) prophylaxis according to American College of Chest Physicians guidelines. The remaining 22 patients were treated with graduated compression stockings and began anticoagulation with heparin immediately upon diagnosis. Patients were treated with heparin for a mean of 7.4 days (range 3–24) prior to surgery. Heparin was continued until a mean of 8.5 hours preoperatively and was resumed at a mean of 10 hours postoperatively. Sixteen patients were treated with intermittent pneumatic compression stockings during and after surgery. In two patients, an IVC filter was inserted preoperatively. Postoperatively, six (27%) patients had improvement in their DVT. In 10 (46%) patients, the DVT was unchanged and in six (27%) patients, there was progression of the DVT, including two of 22 patients (9%) with clinical deterioration, which was defined as development of pelvic DVT or PE. They recommended shorter or no interruption in heparin therapy and greater use of IVC filters.

Hoffman et al reported on the management of 12 patients with gynecologic malignancy that presented with DVT over a 3-year period.[16] Management was at the discretion of the attending physician. IVC filter placement was attempted in 10 patients, but was unsuccessful in two due to tumor compression of the IVC. Both of these patients underwent IVC ligation intraoperatively. One of these patients, who had massive intra-abdominal tumor burden, died of intraoperative cardiac arrest approximately 1 hour after the IVC ligation was performed, possibly due to pulmonary embolism. Seven of 10 patients were treated with at least 1 week of intravenous heparinization prior to attempted IVC filter placement. Heparin was stopped 2–4 hours preoperatively. Only three patients were treated with heparin postoperatively. One of these patients was uneventfully bridged to warfarin therapy for 6 months. A second patient was not started on heparin until postoperative day 3, when she developed progression of her thrombosis. Heparin was stopped on postoperative day 9, when she developed a left groin hematoma, requiring return to the operating room. The third patient developed HIT and severe hemorrhage from her endometrial cancer. These investigators recommend 14 days of heparin therapy preoperatively to stabilize the clot with IVC placement to prevent pulmonary embolism intraoperatively.

Abid et al described the use of preoperative IVC filter placement in 39 patients with gynecologic cancer and venous thromboembolism diagnosed preoperatively who required major surgery.[17] Of these patients, 17 (39%) underwent surgery within 6 weeks of the diagnosis of thrombosis. Patients did receive therapeutic anticoagulation prior to and after filter placement. The night prior to their gynecologic surgery, patients were treated with a prophylactic dose of LMWH. A sequential compression device was applied to the unaffected limb during surgery. Postoperatively the patients were treated with a sequential compression device to the unaffected limb, early ambulation, and prophylactic doses of LMWH. No patient had a worsening of her thrombosis and there were no filter-related complication. The authors note that a short interval between the

diagnosis of VTE and surgery was not associated with increased perioperative morbidity.

At Vanderbilt, our general practice for a patient needing surgery for a gynecologic malignancy who presents with a venous thromboembolism is to treat with therapeutic heparin or LMWH for 14 days preoperatively, when possible, to stabilize the clot. An IVC filter is placed at the time of surgery. Heparin is discontinued 6 hours preoperatively and LMWH is discontinued 12 hours preoperatively. Therapeutic anticoagulation is resumed 12 to 24 hours postoperatively, when we are assured that there are no bleeding complications. Patients are discharged to continue therapeutic anticoagulation with LMWH for at least 3 months for those with DVT and for at least 6 months for patients with PE. However, anticoagulation is not discontinued until treatment is completed and the patient's cancer, the underlying cause of the thrombosis, is confirmed to be in remission. It is important to keep in mind that Trousseau's syndrome is warfarin-resistant. Also, IVC filters may not be completely protective in Trousseau's syndrome, as clots can form anywhere in the venous system, not just in the pelvis and lower extremities.

Although uncommon, HIT is a life-threatening complication of anticoagulation with heparinoids. There is a paucity of data to guide its management in the perioperative setting. Doepker and colleagues evaluated risk factors for hemorrhage associated with argatroban therapy in the critically ill.[18] Major surgery prior to or during argatroban therapy was associated with the highest risk of hemorrhage, relative risk 8.4 (95% confidence interval [CI], 2.3–30.1; $P = .001$). In all, 27 patients receiving argatroban therapy for HIT underwent surgery, with 10 (37%) undergoing an abdominal procedure. Of these, five (41.7%) experienced a bleeding event. Bleeding complications were most common in patients following cardiac surgery. Hoffman et al recommended reducing the initial argatroban dose to 0.5 μg/kg/min, adjusted to achieve therapeutic activated PTTs to decrease the risk of bleeding in patients post-coronary artery bypass graft surgery.[19] This strategy might be applied to post-abdominal surgery patients, as well.

Peripheral primitive neuroectodermal tumors (pPNETs) are part of the Ewing's sarcoma family of tumors. These tumors are most commonly associated with fusion of the *EWS* gene on chromosome 22q12 with various members of the *ETS* gene family. In rare cases, *FUS* can substitute for *EWS*, resulting in fusion transcripts with no *EWS* rearrangement. Ewing's sarcoma also is characterized by strong expression of the cell surface glycoprotein MIC2 (CD99). Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (CAV/IE) is the preferred regimen for patients with localized disease. For patients with metastatic disease, vincristine, doxorubicin, and cyclophosphamide is the preferred regimen.[20]

In the ovary, there also may be central neuroectodermal tumors that are monophasic teratomas. The poorly differentiated or primitive forms of these tumors (cPNET) include medulloblastoma, medulloepithelioma, neuroblastoma, and ependymoblastoma.[21] These tumors are distinct from pPNETs and typically do not demonstrated the Ewing's chromosomal translocation. They do not or only focally express CD99.[21–23] These patients are often managed by extrapolation from the experience in transformed male germ cell testicular tumors with cisplatin-based regimens, such as bleomycin, etoposide, and cisplatin (BEP).[22] Demitras et al reported a case of a 25-year-old woman with cPNET arising in the ovary, which was initially treated with BEP. Persistent disease was identified at second-look laparotomy performed 3 months after the completion of treatment. She was treated with salvage vinblastine, ifosfamide, and cisplatin. Following this, she had two successful pregnancies and was without evidence of disease for more than 4 years.[24] Other investigators have suggested that, despite arising in germ cell tumors, cPNETS are resistant to cisplatin.[25,26] Alternate regimens, such as CAV/IE, have been recommended.[26]

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DISCUSSION

Presented here is a difficult case of an aggressive ovarian tumor necessitating the emergent surgical treatment of a patient with acute onset of lower extremity thrombosis and bilateral pulmonary emboli who also quickly developed HIT during anticoagulation.

In general, the National Comprehensive Cancer Network (NCCN) and American College of Clinical Pharmacy (ACCP) guidelines offer specific criteria in assessing clinicans' suspicion toward the likelihood of HIT in patients, and offer recommendations for the utilization of specific thrombin inhibitors US Food and Drug Administration (FDA)-approved for the prevention of thrombosis, as well as therapy of existing thrombosis when likelihood of heparin sensitivity is high.[27] Following Warkentin's key text,[5] a pre-test probability score can be estimated, and a direct thrombin inhibitor may be started

while confirming the diagnosis of HIT and removing heparin-based medications from the patient's system. Specifically, argatroban, derived from L-arginine, is the only anticoagulant approved for both interventional and non-interventional settings for patients diagnosed with HIT. Argatroban is hepatically metabolized and can be used safely in patients with renal disease.[27] An additional agent that can be considered in the treatment and prevention of HIT is fondaparinux (barring adequate renal function), but its half-life is longer, and its use preoperatively may not be considered as feasible given bleeding risks; additionally parenteral direct thrombin inhibitors are "preferred" in the NCCN guidelines.[5]

While warfarin- and heparin-based anticoagulants are well understood, and their use well established during the perioperative period, we acknowledge that there currently is scant literature on the use of argatroban in the perioperative period, especially during a case of emergent surgery. In addition, to our knowledge, there is no specific mention of the use of argatroban in a case of HIT in the gynecologic literature.

Argatroban's use for perioperative anticoagulation in a patient with a history of HIT is described in the literature as a tool for bridging therapy in a patient with atrial fibrillation undergoing carotid endartectomy, who also had a history of HIT.[27] For this patient, warfarin was discontinued 48 hours prior to the surgery, while argatroban (2 μg/kg/min) was infused continuously before, during, and for 4 days postoperatively. During the procedure, argatroban was adjusted at 0.25 μg/kg/min increments to maintain the activated clotting time at or above 200 seconds. The patient was subsequently bridged to warfarin and argatroban was discontinued when the INR was recorded at 2.0.

For long-term anticoagulation in patients with HIT, argatroban can be transitioned to warfarin therapy once the platelet count has reached at least 150,000/μL.[8] There should be at least 5 days of combination argatroban-warfarin therapy with a goal INR to 2.0 to 3.0, before the argatroban can be discontinued.[8] Warfarin therapy should be continued for at least 2–3 months in HIT patients who do not experience a thrombotic event, at least 3–6 months in patients with HIT and a thrombotic event, and potentially extended further in a patient with a malignancy.[7] Newer oral anticoagulants, including rivaroxiban, have not specifically been tested in cancer patient and thus would warrant further investigation.

This case describes a unique situation where familiarity with non-heparin anticoagulants was imperative. As it takes 100 days for HIT antibodies to resolve, and the safety of desensitization of heparin products is not well established,[27] it is important to increase our knowledge of the use of argatroban in the gynecological oncology field due to the prospect for an oncology patient who has been exposed to heparin requiring emergent surgery. As Drs Cromwell and Crispens indicate, it is ideal to treat a new venous thromboembolism for at least 2 weeks prior to embarking upon invasive surgery in order theoretically to ensure clot stability, but this indeed depends also on the urgency of surgical intervention. In this instance, a direct thrombin inhibitor with short half-life is reasonable in order to decrease the risk of hemorrhage upon surgical intervention. Placement of an IVC filter remains a topic of controversy, and as Dr Cromwell states, the balance of bleeding and clotting in patients with thrombophilia is a matter of clinical judgment and experience.

In addition, long-term anticoagulation will need to be revisited regularly while undergoing chemotherapy treatment. As discussed by Dr Crispens, determining whether a PNET may originate peripherally or centrally (and whether cytogenetically related to a Ewing's-type of sarcoma) may guide choice of treatment, but case reports may indicate disparate sensitivities to various regimens. This rare type of tumor arising in neuroendocrine tissue requires further understanding at the molecular level. The patient presented here also has a significant family history of breast cancers, as well as VTE, and would warrant further investigation as to the likelihood of a hereditary mutation in tumor suppressor gene(s), and/or genetic propensity for thrombophilia.

We appreciate the discussion of this challenging case and welcome your comments.

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