Venous Thromboembolism in a Gynecologic Cancer Patient

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Mrs. S. is a 37-year-old Caucasian female who sought care at her home institution overseas during a period of several months for complaints of esophageal reflux, constipation, early satiety, increasing abdominal girth, and fatigue. Upon presentation at her home institution, her weight was 237 pounds, with a body mass index (BMI) of 42.77 kg/m². Nutritional consultation was obtained to facilitate weight loss and the patient was prescribed a bowel regimen for constipation.

Six months after initial presentation, the patient developed dyspnea, orthopnea, and right-sided pleuritic chest pain. Chest radiography revealed a right-sided pleural effusion, prompting a computed tomography (CT) scan of the chest. The CT scan was negative for pulmonary embolus (PE), but it confirmed the right-sided pleural effusion and revealed upper abdominal ascites. Further evaluation by abdominal and transvaginal ultrasound documented a large pelvic mass. Diagnostic thoracentesis identified adenocarcinoma cells of unknown origin, while paracentesis was inconclusive.

The patient was air-evacuated from her home overseas to our practice in the United States for definitive diagnosis and management. Upon arrival, CT scan of the abdomen and pelvis revealed an adnexal mass of approximately 25 cm, most likely arising from the right ovary; abdominal ascites; and omental caking suggestive of ovarian adenocarcinoma. Repeat CT of the chest was again negative for pulmonary embolism (PE).

During the evening of hospital day five, the patient became acutely dyspneic, cyanotic, and tachycardic. CT revealed extensive bilateral emboli which were most prominent in the branches of the right pulmonary artery, as well as a large left-lower-extremity deep venous thrombosis (DVT).

TREATMENT

Following her diagnosis of DVT and PE, Mrs. S. was transferred to the intensive care unit and stabilized on an intravenous unfractionated heparin sodium drip. Given the acute thromboembolic event and the resultant need for continuing anticoagulation, surgical exploration of the pelvic mass was deferred because of concern about intraoperative hemorrhage and progression of thrombosis. Instead, neoadjuvant paclitaxel (Taxol) and carboplatin chemotherapy was initiated.

On hospital day six, an inferior vena cava (IVC) filter was placed to address the patient’s continuing high risk of further thromboembolic events. Additionally, Mrs. S. received her first cycle of chemotherapy. By hospital day eight, she was transitioned from intravenous unfractionated heparin to a once-daily fondaparinux sodium (Arixtra) bridge. Long-term warfarin sodium (Coumadin) therapy was also initiated. In anticipation of intravenous port placement on hospital day 10, however, the warfarin sodium therapy was discontinued and the patient instead was placed on twice-daily enoxaparin sodium (Lovenox).

Following completion of her treatment, Mrs. S. returned home overseas, where she underwent three uneventful cycles of paclitaxel and carboplatin, with growth factor support. She remained active by walking daily, maintaining her home, caring for her teenaged daughter, and returning to work part-time as a waitress. Therapeutic anticoagulation continued with enoxaparin sodium injections. Three months after her first transatlantic flight, Mrs. S. returned to the United States for the planned staging and debulking surgery. Conscious of her persistent venous thromboembolic risk, she wore compression stockings during the flight, and she continued twice-daily enoxaparin sodium injections through 7 am on the day prior to the surgery. Her intraoperative course was notable for the successful debulking of a 22-pound mass during a 6-hour procedure. Therapeutic anticoagulation resumed with enoxaparin sodium on post-operative day one.

On postoperative day three, Mrs. S. developed edema of the left upper extremity, extending from the subcutaneous port site and encompassing the left basilic, brachial, axillary, subclavian, and internal jugular veins. This massive upper-extremity DVT triggered compartment syndrome of the...
left arm. The intravenous port was removed without incident and the compartment syndrome resolved. Therapeutic anticoagulation was maintained using twice-daily dosing of enoxaparin sodium, and intravenous access was reestablished with a right-sided indwelling catheter. Final pathology from the patient’s debulking surgery was consistent with moderately differentiated mucinous adenocarcinoma of the ovary.

OUTCOME
Mrs. S. returned to her home overseas to complete the last two cycles of adjuvant chemotherapy (she received a total of six) and to begin treatment with consolidation bevacizumab (Avastin) every 21 days. After 6 months of consolidation targeted therapy, and despite long-term anticoagulation therapy, Mrs. S. suffered a fatal PE. She died 10 months following her initial diagnosis and 20 months after the initial appearance of symptoms.

NURSING MANAGEMENT
The American Cancer Society estimates that 21,550 new cases of ovarian cancer were diagnosed in 2009 and approximately 14,600 women died from the disease. Despite its presentation in our 37-year-old patient, Mrs. S., ovarian cancer is predominantly a disease of older women. In 2002–2006, approximately 12% of ovarian cancers were diagnosed in women younger than 45 years of age, and the median age at diagnosis was 63 years. Ovarian cancer affects Caucasian women predominantly, with an age-adjusted incidence of 13.8 per 100,000 women. In the United States, the median age at death from ovarian cancer was 71 years old, with a mere 3.8% of deaths occurring in women younger than 45 years old. Recently, an association between ovarian cancer and obesity, presumably mediated through the hormonal influences of adipose tissue, has been confirmed.

Presenting symptoms for ovarian cancer can often be vague and misleading, and frequently can mimic other conditions, as in our patient’s case. Constant, progressive gastrointestinal symptoms that are not related to specific foods can help distinguish ovarian cancer symptoms from those of gastrointestinal conditions. Repeated visits for similar and/or worsening complaints over a period of time should alert the medical care team that further diagnostic testing may be warranted. Nurses in the primary care setting have a unique opportunity to monitor patient visits for such patterns, which may suggest incomplete diagnosis or psychiatric illness, or may represent domestic violence. The case of Mrs. S. illustrates multiple features crucial to the nursing management of oncology patients with venous thromboembolism. Nurses are instrumental in the identification and mitigation of risk factors for VTE in their patients. Our patient’s risk factors for PE included her history of ovarian cancer, her prior diagnosis of VTE, stasis secondary to air travel, cancer staging with a lengthy debulking surgery, indwelling intravenous catheterization, chemotherapy that included antiangiogenic therapy, and obesity. While the risks associated with ovarian cancer, history of PE, and surgery certainly cannot be entirely mitigated, the nurse case manager can provide patient education and interventions aimed at addressing the remaining risk factors.

Nurses can ensure that patients are properly informed about the risks associated with air travel, and that they have appropriate recommendations for risk-reduction if they do intend to travel, as in the case of Mrs. S. Furthermore, nurses are instrumental in managing the day-to-day habits of their patients, and nursing management should include teaching patients about self-administration of injections and proper outpatient usage of prophylactic medications. Nurses can also ensure that their oncologic patients are maintaining healthy diet and exercise routines; this becomes particularly important with the administration of chemotherapy. Finally, in the inpatient setting, nurses are exceptionally situated to risk-stratify their patients and thereby ensure that mechanical prophylaxis (eg, use of compression stockings) and chemoprophylaxis are instituted in an appropriate and timely fashion.

DISCUSSION
In 1865, Trousseau first described the association between cancer and venous thromboembolism (VTE). Since that initial observation, the medical community has struggled with the challenge of the diagnosis, prevention, and treatment of VTE in patients with malignancy. Virchow’s triad of hypercoagulability, stasis, and endothelial injury forms the foundation of modern understanding of the pathophysiology of VTE and this understanding drives current concepts regarding management.

Venous thromboembolism is a critical public health issue, with an incidence of between 117 and 148 cases per 100,000 in the general population. Oncology patients experience VTE four times more often than their contemporaries who do not have cancer. Risk factors are necessary features of the disease, with 96% of patients diagnosed with VTE exhibiting at least one risk factor and 76% demonstrating two or more risk factors. Risk stratification of hospitalized
patients reveals that the vast majority demonstrate a minimum of one risk factor for VTE.[13] Obesity is one established risk factor for venous thromboembolism.[11–15] Obesity is also strongly related to coronary artery disease and stroke, and these diagnoses comprise the two most common disorders of the cardiovascular system. Mechanisms driving VTE in obese patients include increased procoagulant factors, platelet aggregation, and inhibited fibrinolysis, and the extent of these alterations has been correlated to body mass index (BMI).[12] Other anthropometric variables that have been studied with respect to risk for VTE include body weight, waist and hip circumference, and bioelectrical impedance, which is used to calculate total body fat mass. In addition to BMI, these surrogate measurements of obesity serve as statistically significant predictors of increased risk for VTE.[17]

Age is a known risk factor for VTE, with incidence of the disease increasing exponentially with increasing age.[11,13–15,18] Patients 85 years of age and older experience a 15-fold increased risk of VTE in comparison to their counterparts younger than 55.[18] Another significant risk factor for VTE is history of prior PE or DVT.[13–15] Indeed, VTE is a chronic disease process which is likely to recur. In patients with unprovoked VTE, rates of recurrence have been reported to be 20%–41%, with further increases demonstrated over time.[18] Cancer patients in particular experience a high risk of recurrence.[7,14] The risk of VTE recurrence is also related to obesity; patients with higher BMI have higher rates of recurrence than their leaner counterparts.[12] Surgery confers increased risk of provoked VTE when compared with no surgery,[11,13] and VTE represents a potentially avoidable complication of the perioperative period.[19] Though the incidence of VTE in the absence of surgical prophylaxis remains unknown, estimates have been derived from data obtained prior to its consistent use. In this setting, rates of DVT averaged 15%–30%, while rates of fatal PE approached 0.2–0.9%.[6] Patients with the highest risks of postoperative VTE include patients undergoing orthopedic surgeries and cancer patients.[6,15,20] In the 6 weeks after an inpatient surgical procedure, the postoperative relative risk of VTE is increased by more than 69 times the baseline nonsurgical rate, with the peak incidence of thromboembolic events occurring in the third postoperative week.[20] Surgical risk for VTE persists beyond the sixth postoperative week, with approximately a 20-fold increased risk at 12 weeks and a 9% risk at 6 months.[20] Gynecologic surgery, even in the absence of malignancy, results in excess VTE risk comparable to that of general surgery patients, while gynecologic oncology patients encounter still greater risk.[7,11,13,15]

Long-distance travel generates increased risk of VTE, particularly in patients with additional risk factors.[13] For low-risk travelers on flights longer than 8 hours or travelers with moderate risk (ie, those with risk factors for VTE), adequate hydration, frequent calf muscle contraction, and avoidance of constricting clothing has been recommended. Conversely, in travelers deemed to be of the highest risk, in whom active prophylaxis is required, graduated compression stockings or single-dose chemoprophylaxis should be considered.[13]

Oncology patients form a particularly vulnerable population with respect to venous thromboembolism in that they encounter risks attributable to all arms of Virchow’s triad.[5,6,8] Indeed, cancer increases risk of VTE, with approximately 20% of oncology patients suffering from thromboembolic events associated with their malignancy.[5,10] Autopsy studies predict even higher rates of VTE, up to 50%–60%, in patients dying with cancer.[5,8,11,14] Pulmonary embolism has been found to be the single most common cause of postoperative mortality in surgical, urologic, and gynecologic oncology patients,[19] and VTE is among the leading causes of death in patients with malignancy.[9,15,21] In cancer patients, VTE follows a more volatile course, and treatment failures with conventional therapies are high.[21]

Cancer patients are presumed to experience endothelial injury secondary to tumor burden, concomitant infection, long-term central intravenous access, general anesthesia, surgical trauma and manipulation, chemotherapeutic medications, and radiation, among other causes.[13,14] Indwelling venous catheters increase the risk of VTE by 5.6-fold, and the use of such catheters is common in patients with malignancy.[6,14,15] Cytotoxic, hormonal, and antiangiogenic chemotherapy also contributes to an excess VTE risk,[11,13,22] with reports of a 6.5-fold higher risk in chemotherapy patients compared with the general population and a 4-fold higher risk compared with cancer patients not undergoing chemotherapy.[6,14] Colony-stimulating factors designed for bone marrow support exacerbate VTE risk in chemotherapy patients.[6,14,22] Oncology patients are subject to higher risks of venous stasis since they are often bedridden after surgery or debilitated by their illness.[11] They undergo longer and more complex surgeries, and frequently undergo multiple procedures. Excess risk of VTE continues secondary to the cancer diagnosis, as patients with cancer experience higher rates of VTE than noncancer patients when controlling for type of cancer present.
Hypercoagulability in cancer patients is mediated by increasing circulating procoagulant substances released or promoted by malignant cells, by the coagulation cascade, and by systemic endothelial cell activation. Furthermore, type of cancer affects rates of VTE, with ovarian cancers conferring a high risk at a VTE rate of 12 per 1,000 patients. Finally, VTE seems to be associated with worsened survival when present in patients with malignancy. Perioperative anticoagulation provides a unique opportunity for effecting adequate prophylaxis. Prophylaxis has been demonstrated to reduce the incidence of VTE and of fatal PE, with acceptable risk profiles for clinically significant hemorrhage and for cost, though rates of VTE remain high in gynecologic oncology patients when dual prophylaxis is not utilized. The American College of Chest Physicians (ACCP) provides guidelines for perioperative risk stratification for the prevention of VTE. Surgical patients are divided into groups based on risk factors, and prophylactic anticoagulation strategies are outlined based on stratified risk. Thromboprophylaxis is recommended for all oncology inpatients, with particular attention toward extended (outpatient) prophylaxis in high-risk cancer patients, such as after surgery. In the gynecologic oncology patient population, dual-prophylaxis protocols designed per the ACCP guidelines have demonstrated significant (70%) reduction in VTE incidence over single-agent prophylaxis with acceptable rates of bleeding complications.

Chemoprophylaxis in the oncology setting has typically favored low-molecular-weight heparin (LMWH) preparations because of ease of administration, lower risk of heparin-induced thrombocytopenia (HIT), and predictable pharmacology which does not require laboratory monitoring. Long-term warfarin therapy inherently poses significant challenges for patient management: recurrence risk for VTE is two to three times as likely even in the setting of strict maintenance of therapeutic levels. Furthermore, warfarin introduces higher risks of bleeding in the setting of thrombocytopenia, its longer half-life complicates procedural scheduling and allows for wide fluctuations in levels with changes in diet and clinical condition, and patients on warfarin therapy require constant laboratory monitoring. Compared with warfarin, LMWH has been shown to statistically significantly reduce VTE risk by 52%. For gynecologic oncology patients, chemoprophylaxis with low-dose unfractionated heparin three times daily has been demonstrated to be equivalent to LMWH for surgical prophylaxis with equivalent bleeding risk, while the twice-daily dosing of unfractionated heparin was noted to be ineffective. Another study revealed no difference between intermittent pneumatic compression devices and LMWH with respect to symptomatic VTE. Post-discharge chemoprophylaxis should be considered in the highest risk patients, as one randomized, blinded trial revealed a 60% relative risk reduction when 1 month of LMWH was compared with 1 week of postoperative anticoagulation. In other investigations, dosage is proportional to efficacy. One study revealed a 50% reduction in VTE risk with 5,000 units of dalteparin (Fragmin) compared with 2,500 units, though this benefit was at the expense of a doubled rate of major bleeding complications. Survival, thought to be secondary to suppression of growth and metastasis, may also be influenced by thromboprophylaxis with LMWH, though evidence is conflicting and survival improvement has been reported with warfarin use as well. In patients with metastatic or advanced solid-organ disease surviving at least 17 months, survival was statistically significantly improved at 2 and 3 years in patients receiving once-daily dalteparin vs placebo. Another study revealed that for patients with nonmetastatic disease, LMWH conferred a survival advantage when compared with vitamin K antagonist therapy, although the difference and survival did not persist for patients with metastatic disease.

Despite advances in medical understanding of the pathophysiology of VTE, diagnosis and management of this disease remain a challenge in all patients, but are particularly complicated in oncology patients. Careful risk stratification and targeted prophylaxis and therapy should be instituted in these patients to mitigate their excess risk of VTE. Oncology nurses are crucial in the care of cancer patients, and specifically, with respect to VTE.

**Practice Pearls**

- Thromboprophylaxis is recommended for all oncology inpatients, and extended (outpatient) prophylaxis is recommended in high-risk cancer patients (eg, after surgery).

- Chemoprophylaxis in the oncology setting has typically favored low-molecular-weight heparin (LMWH).

- For gynecologic oncology patients, chemoprophylaxis with low-dose unfractionated heparin TID has been demonstrated to be equivalent to LMWH.

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