Deep Vein Thrombosis in the Patient With Cancer

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Case Study

Ms. L, age 76, was diagnosed in January 1998 with locally advanced (III-B) breast cancer that was estrogen/progesterone receptor negative and positive for the HER2/neu oncogene. After undergoing a left mastectomy, she received adjuvant chemotherapy with doxorubicin and cyclophosphamide. In 1999, disease recurrence on the chest wall was treated with paclitaxel and trastuzumab, followed by palliative radiation therapy to the chest wall. A left partial acromioplasty was performed in February 2000 to manage extension of the disease from the chest wall. The patient then remained stable until this morning when she awoke with chills and a fever of 102°F. She reported that she had cough and says that she stays in bed or on the sofa all day.

Physical examination reveals an awake, alert, anxious, slightly confused patient short of breath at rest. Her vital signs are: temperature = 101.6°F; pulse = 120/minute and regular; respiratory rate = 30/minute; and blood pressure = 190/95 mm/Hg. Her oxygen saturation is 86% on room air and 92% on two liters of oxygen per nasal cannula. She has decreased breath sounds at the right base. Her abdomen is soft and nontender with normoactive bowel sounds. Pitting edema (grade 2 out of 4) is evident bilaterally in both ankles and to the knee on the right. The right leg also is pink and warm to the touch. She has grade 2 (out of 4) tender with normoactive bowel sounds. Pituitary hypoplasia is made, and therapy is initiated.

Thromboembolic disease includes superficial and DVT, pulmonary emboli, thrombosis of venous access devices, and arterial embolism. This disease affects 15% of all patients with cancer and is the second leading cause of death in hospitalized patients with cancer (Haire, 2000; Letai & Kuter, 1999). If the cancer is diagnosed at the same time or within one year of the thromboembolic event, it tends to be at a more advanced stage and the prognosis is considered poor (Sorensen, Mellemkjaer, Olsen, & Baran, 2000). 1. Lower extremity DVT is the most common manifestation of thromboembolic disease. Which of the following is a persistent risk factor for development of lower extremity DVT in Ms. L?

A. Prior surgery
B. Immobility
C. Prior chemotherapy treatment
D. Her underlying tumor

2. Based on knowledge of the treatment of choice in the initial management of acute DVT, the nurse prepares to teach Ms. L about which of the following treatments?

A. Fibrinolytics
B. Unfractionated heparin (UFH)
C. Low molecular weight heparin (LMWH)
D. Vena cava interruption

3. On day six, Ms. L’s platelet count fell to 43,000/mm³. Which complication of anticoagulation administration should the nurse suspect?

A. Thrombotic thrombocytopenic purpura
B. Heparin-induced thrombocytopenia with thrombosis (HITT)
C. Heparin allergy
D. Heparin rebound

Discussion

Question 1: The correct response is choice D. Inherited or acquired abnormalities of the hematopoietic system and cancer are considered to be persistent risk factors for the development of thromboembolic disease (Alatri, Carovalu, & Prandoni, 2000). For this reason, treatment recommendations for patients with cancer include continuing DVT treatment until no evidence of the disease exists and not limiting treatment to 6–24 weeks for a first DVT as is recommended for patients with nonmalignant disease (Bauer, 2000).

Cancer and its treatment can affect all three arms of Virchow’s triad, which include....
damage to vessel endothelium, alteration in blood flow, and increased production of procoagulants (Daugherty, 2000; Hickey, 1998). Tumors or chemotherapy can damage endothelial cells lining the blood vessels. Damaged endothelium is unable to perform its usual anticoagulant and fibrinolytic functions (Daugherty) and may release substances that enhance thrombosis (Hickey).

Alteration in blood flow is caused by the mechanical effects of the tumor on blood vessels, as well as the creation of new blood vessel complexes that result from tumor angiogenesis. In addition, increased amounts of tumor-associated procoagulants often are found on the surface of cancer cells and in the bloodstream of patients with cancer. Examples of these are cancer procoagulants (cysteine proteases not found in normal cells), which directly activate factor X (Gordon & Cross, 1981), and a tissue factor procoagulant (found in normal cells) that appears to activate the clotting mechanism through the extrinsic pathway by binding and activating factor VII (Al-Mondhiry, 1984).

Choices A and B are incorrect. Patients with cancer often have many risk factors for DVT, including advanced age, prior surgery (choice A), immobility (choice B), hormone therapy, and indwelling central venous catheters. However, except for age, these risk factors have the potential to be limited to the course of the patient's illness and are not persistent risk factors.

Choice C is incorrect because in the majority of patients, chemotherapy is not a persistent ongoing event. Although many thromboembolic events do occur during or shortly after chemotherapy, Ms. L had not had chemotherapy since 1999. Levels of fibrinopeptide A have been shown to increase during chemotherapy infusions (Haire, 2000). This substance is associated with the rapid conversion of fibrinogen to fibrin. Also, a decrease in naturally occurring plasma proteins with anticoagulant properties, such as antithrombin III, protein C, and its cofactor protein S, has been observed with the administration of cytotoxic, anti-metabolic, and hormonal chemotherapy (Haire; Letai & Kuter, 1999). Decreases in these proteins are believed to contribute to thrombotic events that occur both during and after the completion of chemotherapy administration (Haire; Letai & Kuter).

**Question 2: The correct answer is choice C.** The goal of treatment for a patient with acute DVT is to prevent the thrombus from enlarging or embolizing. Anticoagulation is the best way to accomplish this in most cases. In patients with cancer, concerns arise regarding the increased risk of hemorrhage because of the tumor itself, thrombocytopenia, or other coagulation disorders. Therefore, optimal anticoagulant selection is critical. Heparin (e.g., LMWH, UFH) is an anticoagulant with antithrombotic properties that warfarin lacks. It also affects angiogenesis, activity of procoagulants, immune function, and gene expression in ways that may impede tumor growth (Letai & Kuter, 1999; Zacharski, Ornstein, & Mamourian, 2000). Initial treatment of DVT consists of approximately five days of heparin administration, as it confers an immediate anti-thrombic effect.

LMWH has documented benefits over standard UFH and may become the new standard of treatment for venous thromboembolism in the United States. Many healthcare providers consider LMWH to be safer, more convenient, more effective, and less expensive if hospitalization can be avoided (Ansell et al., 2000; Haire, 2000). LMWH is equivalent to UFH with respect to thrombus regression, as well as prevention of recurrence (Rodgers & Spiro, 1999). A 1995 meta-analysis of 10 trials found LMWH to be more effective than UFH in reducing thromboembolic complications, bleeding, and mortality (Lensing, Prins, Davidson, & Hirsh, 1995).

LMWH is derived from chemical or enzymatic degradation of UFH and is composed of a smaller molecule that allows it to be more readily absorbed after subcutaneous administration (Ansell et al., 2000). Bioavailability of LMWH is more than 85%, compared to 15% for UFH. Its plasma half-life is 3.5–4.5 hours, compared to 1.5 hours for UFH (Letai & Kuter, 1999). This high bioavailability and longer half-life allow for once or twice daily subcutaneous dosing schedules as opposed to the continuous IV administration required when UFH is used (Ansell et al.). In uncomplicated cases, hospitalization can be avoided, thereby mitigating its increased cost over UFH. Also, costs are reduced because monitoring the partial thromboplastin time is not necessary, as this test is not usually prolonged by LMWH (Greaves, 2000). If monitoring the extent of anticoagulation in a patient with LMWH is important, an assay measuring the level of inhibition of factor Xa activation can provide some limited information regarding antithrombic effect and bleeding risk. Some recommend that anti-Xa levels be measured once at the beginning of treatment for established DVT to ensure adequate anticoagulation, but routine monitoring currently is not indicated (Greaves; VanCoth & Laposata, 2001). (A level of approximately 0.4–1.1 U/ml generally is considered therapeutic for twice a day dosing; somewhat higher levels are required for once a day dosing [VanCoth & Laposata].) In addition, because a fixed dose of LMWH is administered based solely on the patient’s weight, laboratory testing is not needed to monitor variations in levels resulting from changes in medication or diet (Ansell et al.). Haire (2000) noted that “because of the better biologic and psychosocial outcomes inherent with low molecular weight heparin therapy, these are the agents of choice in the initial treatment of acute venous thromboembolism” (p. 683). Choice C, use of UFH as the initial treatment of DVT, is incorrect because LMWH is considered the best agent to use.

LMWH may be a better choice for long-term management of DVT. Studies have found an increased risk of recurrent thrombosis in some patients on warfarin despite an INR of 2–3 (Bauer, 2000). However, a recent study of 1,303 patients found that adequately dosed vitamin K antagonists (warfarin) are effective in patients with malignant disease when INR was maintained above 2. The rate for bleeding complications also increased when INR was less than 2 in patients with cancer. However, more frequent INR monitoring (every two to three weeks or more) was required to keep these patients within the therapeutic range (INR 2–3) (Hutten et al., 2000). Frequent blood sampling could be a burden for patients with cancer who are very ill, have poor venous access, or live in rural areas. Continued research is being conducted to ascertain which method of long-term anticoagulation is best for this population.

Choice A is incorrect because fibrinolitics have a place in the treatment of pulmonary embolism in both benign and malignant etiology, but their use is controversial in the treatment of DVT, even in patients without cancer. Considering the possible increased risk of bleeding in patients with cancer, fibrinolitics should not be used to treat DVT in this population (Haire, 2000).

Choice D is incorrect because a vena cava interruption device (i.e., inferior vena cava [IVC] filter) is considered an option only if...
when a contraindication to anticoagulation exists. These devices decrease the risk of pulmonary embolization from thrombi in veins distal to the device. However, many patients with cancer develop thrombi in thoracic veins as a result of venous access catheters and nonbacterial thrombotic endocarditis (Haire, 2000). (In extreme cases, this device has been placed in the superior vena cava, but the U.S. Food and Drug Administration has not approved this use and the procedure is technically difficult.) The IVC device does nothing to prevent local extension of a thrombus nor does it correct any underlying coagulation defects. The device itself, when used in the absence of anti-coagulation, may undergo thrombosis, and patients may develop severe venous obstruction because of continued propagation of thrombi.

Question 3: The correct answer is choice B. The term HITT often is used interchangeably with either heparin-induced thrombocytopenia (HIT) or “white clot syndrome.” However, HITT refers to the marked thrombocytopenia that occurs in some patients as a reaction to heparin administration, whereas HITT, or white clot syndrome, refers to thrombocytopenia, as well as the thrombosis that results if heparin administration continues. Because these thrombi appear white in color under the microscope, the name white clot syndrome resulted. HITT is most commonly associated with arterial thrombosis, in actuality, HITT include thrombosis of major limb arteries (at times necessitating amputation), myocardial infarction, thrombotic stroke, and, less frequently, mesenteric or renal artery thrombosis, skin necrosis, adrenal thrombosis, and hemorrhage. These limb- or life-threatening thromboses occur in 36%–50% of patients with HITT (Deitcher, 2001). HITT should be suspected in any patient with decreasing platelet counts, especially when increasing amounts of heparin are required to maintain adequate anticoagulation or in patients with a new or recurrent thromboembolic event despite heparin therapy. A platelet count below 100,000/mm³ merits immediate attention. However, a fall in platelet count may not result in an overt thrombocytopenia (e.g., a fall from 400,000 to 125,000/mm³). Therefore, all patients on heparin require daily platelet count monitoring. If a platelet count falls by 40%–50% or more, heparin should be stopped and alternative treatments should be considered (AbuRahma, Boland, & Witsberger, 1991; Hirsh & Huak, 1996). In addition, nurses must monitor for early signs of thrombus development or worsening of an existing thrombus, such as pain or tenderness in the calf or thigh, superficial vein distention, swelling, warmth, chest pain with shortness of breath, unexplained abdominal or lumbar pain, or changes in the patient’s neurologic status.

No specific risk factors are present for HITT except prior exposure to heparin. Sensitization is not related to dosage, type, or route of heparin. Even patients with heparin-coated catheters and those receiving as little as one unit of heparin per hour are at risk for HITT (Elzer & Houdek, 1998). Age is not a factor; even newborns are susceptible. Any patient who previously has been exposed to heparin (e.g., during a diagnostic procedure) may have become sensitized even though they did not develop HITT initially.

A C-serotonin release assay is a highly specific and sensitive test to diagnose HITT, but it is technically demanding and requires a lengthy processing time. A platelet aggregation assay is less sensitive than the C-serotonin release assay, but results are available within one to two hours. Therefore, this test is used commonly in clinical practice. A positive result is specific for HITT, but a negative platelet aggregation test does not exclude the diagnosis (Brandt, 2001). Other coagulation tests can be used to distinguish HITT from various clotting disorders. In HITT, the fibrinogen level and prothrombin time usually are normal, and the fibrin-split products may be normal or slightly elevated.

Treatment of HITT varies. First, heparin should be stopped immediately; some clinicians use protamine sulfate to reverse the effects of heparin. Protamine sulfate neutralizes the effects of heparin and prevents the antibody-mediated platelet aggregation produced by heparin. Warfarin then may be started, but it should not be used alone for initial therapy. Any thrombus present may grow and embolize before the warfarin becomes effective. Warfarin also has been associated with venous gangrene in patients newly diagnosed with HITT (Warkentin et al., 1997). Therefore, anticoagulation should be initiated with another agent, and warfarin should not be started until the platelet count rises above 100,000/mm³ (Matti & Siegel, 2000). Newer anticoagulants, such as danaparoid sodium, lepirudin, or argatrobol, have been used with some success to treat HITT (Brandt, 2001; Deitcher, 2001; Hirsh & Huak, 1996; Hunter, Lonsdale, Wenham, & Frostick, 1993; Rodgers & Spiro, 1999). However, the U.S. Food and Drug Administration has approved only the latter two agents for use with HITT. Also, danaparoid has shown cross-reactivity with 10%–20% of laboratory serum specimens of patients with HITT, although this has not proven to be a problem clinically (Deitcher).

Arterial thromboses frequently are amenable to thrombectomy, embolectomy, or fibrinolysis. Vena cava interruption may be an appropriate intervention in certain cases. LMWH has been associated with a lower incidence of thrombocytopenia than UFH, but routine use of LMWH for the treatment of patients with HITT is not recommended (Hirsh & Huak, 1996; Rodgers & Spiro, 1999).

Nurses must educate patients prior to discharge. Patients should be taught to alert all healthcare personnel to avoid the use of heparin. Patients may want to obtain a medical-alert bracelet or necklace. If elective surgery is needed, patients should be advised to wait until a negative heparin-dependent antibody test is obtained (about four to eight weeks) (Elzer & Houdek, 1998). In addition, measures to prevent recurrence should be initiated. Normal saline flushes should be used instead of heparin flushes for IV lines, heparin-coated catheters should not be used and should be removed if present,
and LMWH may be a better choice than UFH if anticoagulation is necessary.

Choice A is incorrect because thrombotic thrombocytopenic purpura is a syndrome that causes hemolytic anemia, thrombocyto-
penia, neurologic symptoms, fever, and renal dysfunction and is characterized by thrombotic occlusions of the microcircula-
tion. Its cause is unknown, but the syndrome is associated occasionally with the use of estrogen or pregnancy. Thrombotic thrombocytopenic purpura is a medical emergency because bleeding and clotting occur at the same time.

Choice C is incorrect because HITT is only one manifestation of a heparin allergy. Although rare, other hypersensitivity reac-
tions, such as rash, fever, urticaria, asthma, or local reactions at the injection site, may occur. Choice D is incorrect because heparin rebound is the phenomenon of the heparin effect being reactivated from five minutes to five hours after neutralization with protamine sulfate.

Summary

The association between thromboembolic disease and cancer has long been recog-
nized. Armand Trousseau first brought this association to the attention of the medical profession in 1868 (Haire, 2000). Oncology nurses need to be knowledgeable about pre-
ventive measures, early signs and symptoms, and LMWH may be a better choice than UFH if anticoagulation is necessary.

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