Painful Abdominal Ecchymotic Lesions

Mary Van Zandt, RN, OCN®

Case Study

Ms. B is a 57-year-old female who had a 1.5 mm Clark level IV amelanotic melanoma removed from her right eyebrow in 1998. She was disease free until September 2001, when she presented with a mass below her left mandible; an open biopsy confirmed the recurrence of melanoma. She also was found to have a 7 mm lung lesion that was positive for melanoma. The treatment plan included both chemotherapy and surgery. Prior to initiating chemotherapy, Ms. B underwent a wedge resection of the metastatic lesion in her lung followed by two cycles of dacarbazine, vinblastine, cisplatin, interleukin, and interferon. After completing the initial two cycles, the left submental mass was removed. She then received two additional cycles of chemotherapy.

Ms. B’s therapy was complicated by some anticipated side effects, including fever, intractable nausea, hypokalemia, and hypomagnesemia. After she was admitted to the hospital for cycle three, she developed a staphylococcus sepsis and thrombus of her central venous catheter (CVC). The CVC was removed, and treatment was initiated with antibiotics and warfarin 5 mg per day at bedtime. The international normalization ratio goal was 2.3, and Ms. B’s was maintained at 2.4–2.6 during her therapy. On day six of warfarin therapy, she developed painful ecchymotic lesions with irregular borders across her lower abdomen. Some of the ecchymotic areas had a dark red erythematous flush, and the skin was broken over some of the darkest lesions. The oncologist, oncology clinical nurse specialist, and primary care nurse examined the lesions and reviewed the medication and patient profile for potential causes of the skin lesions. The patient’s laboratory values and other parameters were normal. Warfarin was the only medication that had been added to her therapy that week, which led to the suspected diagnosis of warfarin-induced skin necrosis. The warfarin was discontinued immediately, and Ms. B received vitamin K 5 mg and was started on Lovenox® (Aventis Pharmaceuticals, Bridgewater, NJ) 60 mg twice daily. Protein C and S levels were obtained, and the ecchymotic lesions spontaneously faded over the next two days following the discontinuation of warfarin therapy. Both protein C and S levels were significantly low compared to normal values. These low protein levels, combined with the appearance of the initial lesions and spontaneous fading, confirmed the diagnosis of warfarin-induced skin necrosis. The open lesions eventually healed, and no further sequelae of the skin or subcutaneous tissue appeared. Ms. B was discharged from the hospital several days later following CVC replacement and completion of chemotherapy. Lovenox was discontinued at the time of discharge.

Discussion

Oral anticoagulant therapy can result in several adverse skin manifestations, including ecchymosis, hemorrhagic necrosis, and urticarial eruptions. Warfarin-induced skin necrosis first was described in 1942 and is a rare complication that occurs in 0.1% of the population treated with anticoagulant therapy (Chan, Valenti, Mansfield, & Stansby, 2000; RxList, n.d.; Warkentin, 2001). A brief and simplified review of hemostasis, including the clotting cascade and hemostatic control mechanisms, is necessary to better understand this rare adverse event.

Hemostasis is defined as a sequence of events that stops bleeding. Three mechanisms take place to reduce blood loss: a vascular spasm, platelet plug formation, and blood clotting. The vascular spasm occurs when the arteries and arterioles have been damaged and is triggered by damage to the smooth muscle and stimulation of pain receptors. Platelet plug formation occurs to prevent blood loss in small vessels. Clotting is a complex cascade of reactions that takes place in pathways; each clotting factor activates the next one in a fixed sequence. Twelve clotting factors are known, including calcium ions, several inactive enzymes synthesized by hepatocytes, and the activated forms of several proteins.

Mary Van Zandt, RN, OCN®, is a clinical research coordinator for Impath Predictive Oncology at the Hematology/Oncology Centers of the Northern Rockies in Billings, MT. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.)

Digital Object Identifier: 10.1188/02.CJON.363-364
various molecules associated with platelets or released by damaged tissue. Clotting factors most often are identified by a Roman numeral that indicates the order of their discovery. The clotting cascade involves an extrinsic, an intrinsic, and a common pathway. Blood clotting can be divided into three stages:

- The formation of prothrombinase (prothrombin activator) is initiated by either one or both of the extrinsic and intrinsic pathways.
- Prothrombinase and calcium convert prothrombin (i.e., a plasma protein formed in the liver) into the enzyme thrombin. This takes place in the common pathway of the cascade.
- Soluble fibrinogen (i.e., another plasma protein formed by the liver) is converted into insoluble fibrin by thrombin, and the threads of the clot are formed. This occurs in the common pathway of the cascade (Tortora & Grabowski, 2000).

The clotting cascade is more complex, and events can occur over several minutes. Activators are in direct contact with the blood or contained within the blood, and outside tissue damage does not activate this pathway. Damaged endothelial cells of a vessel wall, along with the resulting damaged platelets, release factor XII. The combination of factor XII, platelet phospholipids, and calcium activates factor X. When factor X is activated, it combines with factor V in the presence of calcium and forms prothrombinase. When thrombin is formed, the extrinsic pathway is completed (Tortora & Grabowski, 2000).

The intrinsic pathway begins when activators are in direct contact with the blood, initiating events in the extrinsic pathway by releasing factor XII into the common pathway (Tortora & Grabowski, 2000). The formation of prothrombinase (prothrombin activator) is initiated by either one or both of the extrinsic and intrinsic pathways. The cascade takes place in the common pathway of the cascade.

Frequently, small clots begin to form inside a blood vessel. Because blood clotting involves positive feedback cycles, clots tend to enlarge, creating the potential for impaired blood flow through undamaged vessels. The hemostatic control mechanism or fibrinolytic system dissolves small, inappropriate clots (Tortora & Grabowski, 2000). Included in this system are proteins C and S, which are glycoproteins, as well as several other substances that act as natural anticoagulants. Following activation by thrombin, protein C combines with protein S to break down certain clotting factors. Both are important physiologic defense mechanisms that respond to thrombogenic stimuli; a deficiency of one or both of these proteins leads to altered homeostasis and abnormal clotting (Lee et al., 1999). Although the exact pathophysiology of warfarin-induced skin necrosis is unknown, factor VII deficiency, protein C, and S deficiencies, thrombosis, a direct toxic effect of warfarin, and hypersensitivity all have been suggested (Ad-El et al., 2000; Chan et al., 2000; Ng & Tillyer, 2001).

**Warfarin-Induced Skin Necrosis**

The anticoagulant warfarin is absorbed from the gastrointestinal tract, bound to plasma albumin, and metabolized by the liver (Morsdorf, Berrettini, & Agnely, 1999). Warfarin commonly is used to treat or prevent blood clot formation. Oral anticoagulants actually have an indirect activity by inhibiting vitamin K metabolism in the liver. In the presence of warfarin, y-carboxylation of glutamic acid residues in coagulation proteins becomes defective. This leads to the blocking of the synthesis of clotting factors II, VIII, IX, and X and proteins C and S. These coagulation factors cannot bind with calcium, which is a necessary prerequisite for the formation of prothrombinase and generation of functionally active thrombin. By inhibiting the synthesis of these proteins, the hemostatic balance shifts so that clotting occurs more slowly (Gulba, 1996; Morsdorf et al.). The objective of treatment is to balance the blood-clotting process without causing severe bleeding. Hemorrhaging into any tissue or organ and necrosis or gangrene of the skin and subcutaneous tissue, also referred to as warfarin-induced skin necrosis or Coumadin® necrosis, are serious risks associated with warfarin therapy (Chan et al., 2000; RxList, n.d.; Warkentin, 2001).

Warfarin-induced skin necrosis is the result of extensive thromboembolization of the microvasculature within the subcutaneous fat of the abdomen, buttocks, thighs, breasts, or limbs and is associated with blood clots in areas of tissue damage. Although not common, warfarin necrosis can be a potentially serious side effect of oral anticoagulant therapy and can lead to tissue debridement and even limb amputation if not diagnosed properly (Warkentin, 2001). The condition usually appears 1–10 days after the initiation of warfarin therapy. Although its etiology is unknown, the administration of loading doses of warfarin may cause warfarin necrosis. Other suspected causes include a protein C deficiency, hypercoagulable conditions (e.g., protein S deficiency), factor V Leiden, an antithrombin III deficiency, and lupus anticoagulant. Warfarin necrosis occurs primarily in obese, middle-aged, perimenopausal women (Chan et al., 2000; PDR.net, n.d.). As previously stated, proteins C and S and other clotting factors are part of the natural anticoagulant system, and they function on a negative feedback loop. If these levels are low initially, anticoagulation will not occur normally. In addition, loading with warfarin can lead to a hypercoagulable state because it causes rapid depletion of protein C (New Mexico Heart Institute, 1999), which can lead to thromboembolization. Ms. B’s low protein C and S levels may be related to the fact that she had been taking warfarin before the levels were obtained.

Treatment for warfarin-induced skin necrosis involves early recognition of the problem and close monitoring of this serious side effect when it does occur. Prevention of warfarin necrosis is key in the management of patients taking warfarin. Anticoagulation therapy with heparin for five to seven days during initiation of warfarin therapy may minimize the risk of tissue necrosis (RxList, n.d.). Warfarin loading is not recommended, and the drug should not be administered to patients with known protein C and S deficiencies. Early recognition and diagnosis is important to halt warfarin’s adverse effects. Clinicians should assess skin diligently for signs of ecchymosis or skin disruption, and if they are suspected, warfarin should be discontinued immediately to prevent any sequelae of the event. Vitamin K can be administered to stimulate the production of protein C, and continued treatment with heparin or a low molecular weight heparin is appropriate.

The clotting cascade involves an extrinsic, an intrinsic, and a common pathway.

Affected tissue should be cleansed gently, pressure should be avoided, and nursing measures should maintain skin integrity. Prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, has been used to treat necrotic lesions because it promotes healing. Some patients require surgical debridement of the affected area or extremity, and skin grafting is implicated in some cases (Chan et al., 2000). The affected area should be noted and photographed to indicate any change.

(Continued on page 366)
Ms. B’s case is an example of how early recognition and diagnosis of warfarin-induced skin necrosis can prevent serious sequelae. Although the pathophysiology and etiology of this adverse event are unclear, oncology nurses must recognize factors that place patients at higher risk. Nurses must be aware of warfarin-induced skin necrosis so that it can be identified promptly and treated successfully to maximize patients’ outcomes.

Author Contact: Mary Van Zandt, RN, OCN®, can be reached at maryvanzandt@yahoo.com.

References