CASE STUDY

4 DEEP VENOUS THROMBOSIS

For the Patient Case for this case study, see the printed book.

DISEASE SUMMARY

Definition

Venous thrombosis is a potentially serious, multifactorial disorder of the cardiovascular system that is characterized by the development of intravascular blood clots (i.e., *thrombi*) in both superficial and deep veins. When venous thrombosis occurs within deep veins, the medical phrase *deep venous thrombosis (DVT)* is used. Primarily the deep veins of the calf muscles of the leg (especially the popliteal, peroneal, and posterior tibial veins) are involved. The iliac and femoral veins are also common sites for the formation of venous thrombi. Disease Summary Figure 4.1 shows a thrombus within the lumen of an opened femoral vein.

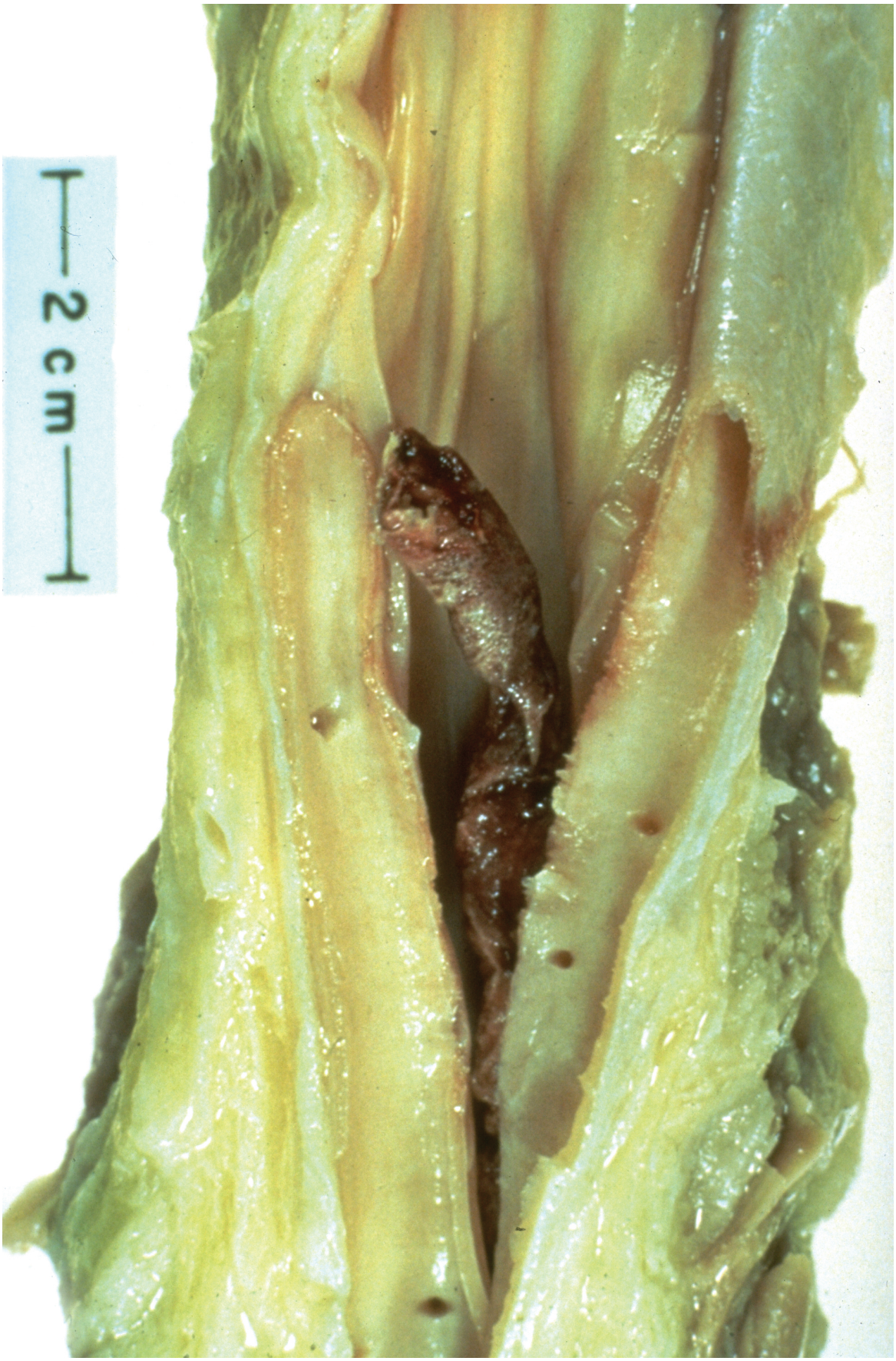
Prevalence

The incidence and prevalence of DVT are unknown, because most cases of DVT are occult and usually resolve spontaneously without complication. However, existing data that underestimate the true incidence of DVT suggest that approximately 80 cases per 100,000 persons occur annually in the United States. The risk for developing DVT in one's lifetime is approximately 5%. However, among hospitalized patients, the incidence of DVT is significantly higher and varies from 20 to 70%. An estimated 600,000 hospitalizations for DVT occur annually in the United States.

The male-to-female ratio for this disorder is 1.2:1. DVT usually affects individuals older than 40 years of age. The condition is expected to increase in prevalence as the elderly population increases.

Significance

The significance of DVT lies primarily in the severe pain that it may cause, in permanent damage to valves in the venous circulation (a condition known as *chronic venous insufficiency* that perpetuates DVT), and in its most serious complication—pulmonary thromboembolism (PTE). PTE may cause death within minutes, *is the leading cause of preventable in-hospital mortality today*, and causes approximately 200,000 deaths annually in the United



Disease Summary Figure 4.1
The femoral vein has been opened to reveal a large thrombus within the lumen. (Reprinted with permission from Rubin E, Farber JL. Pathology. 3rd Ed. Philadelphia: Lippincott Williams & Wilkins, 1999.)

States. As the elderly population increases, the impact of DVT on the nation's healthcare system is also expected to increase. Treatment for DVT is now estimated to cost up to $2.5 billion per year, not including costs associated with its long-term complications.

Causes and Risk Factors

There are many risk factors for DVT, but there are only three major causes of the condition—all of which were identified by a German pathologist, Dr. Rudolph Virchow, in the 19th century. The major causes of DVT, referred to collectively as the *Virchow triad*, are: (a) venous stasis of blood (i.e., stagnant blood flow); (b) increased viscosity or coagulability of blood (i.e., hypercoagulability); and (c) injury to the inner lining (*tunica intima*) of the blood vessel wall. The vast majority of risk factors for DVT are easily explained by the Virchow triad.

Rapid blood flow has an inhibitory effect on thrombus formation, but a slow rate of flow reduces the clearance and dilution of activated clotting factors. *Stasis* tips the delicate balance of procoagulation and anticoagulation toward thrombus formation. Prolonged bedrest is a major risk factor for DVT because it results in poor blood flow and pooling of blood in the lower extremities. People who are bedridden or immobilized as a result of a hip fracture, joint replacement, spinal cord injury, stroke, heart attack, or a lengthy surgical operation are at exceptionally high risk. The elderly are most susceptible because disorders that cause venous stasis occur more frequently with age. Heart failure, in which a poorly functioning heart results in stagnant blood flow, is a common condition among the elderly. Prolonged sitting during extended air travel also poses a significant threat to persons predisposed to DVT.

Hypercoagulability of the blood is caused by any condition that increases the concentration or activation of clotting factors. Mutations in factor V Leiden (occurring in 1/20 Caucasians) and prothrombin 20210A are common genetic abnormalities that have been linked to hypercoagulability. Inherited deficiencies of plasma proteins that normally inhibit thrombosis (e.g., antithrombin III, protein C, and protein S) and excessively high concentrations of factors VIII and XI promote hypercoagulability. In addition, the use of oral contraceptives (especially by women who smoke) and some cancers (primarily lung cancer, but also pancreatic, prostate, breast, and ovarian cancers) are major causes of increased coagulability of the blood. Some cancer cells secrete procoagulant substances that activate the coagulation cascade. Furthermore, patients with cancer often have low levels of protein C, protein S, and antithrombin III.

Pregnancy and childbirth often are associated with DVT because fibrinogen, prothrombin, and other coagulation factors increase during the postpartum period. With dehydration, clotting factors become more concentrated, blood becomes more viscous, and the patient's risk for DVT increases significantly. *Polycythemia vera* is an acquired bone marrow disease that is characterized by an overproduction of all three hematopoietic cell lines, most prominently red blood cells, and poses a risk for both hyperviscosity of the blood and DVT.

Injury to blood vessel walls occurs from trauma, infection, and inflammation. Persons undergoing hip replacement are at significant risk for DVT as a result of surgical trauma to the femoral and iliac veins and from heat generated by the polymerization of the acrylic cement that is used.

Patients with certain autoimmune disorders (e.g., systemic lupus erythematosus and inflammatory bowel disease) suffer from venous thrombosis when production of antiphospholipid antibodies activates both the coagulation cascade and platelet function as well as inhibits the anticoagulant activities of proteins C and S.

Extreme elevations in plasma homocysteine levels, the use of venous catheters, and the introduction of irritating intravenous medications are other relatively significant sources of venous injury. Given the prevalence of these health conditions and procedures, *some patients have more than one risk factor and an additive risk for thrombosis.*

Pathophysiology

Thrombi are composed of variable numbers of platelets, erythrocytes and leukocytes, and fibrin, which provides the meshwork for intravascular blood clots. Trauma to the endothelial cell lining of the vein wall causes exposure of subendothelial tissues to platelets, which adhere and accumulate. Injury and loss of endothelial cells also results in a significant loss of antithrombotic factors (e.g., heparan sulfate). In addition, damaged vascular tissues release tissue thromboplastin, which activates the coagulation cascade. The final steps in the

cascade are the conversion of prothrombin to thrombin and fibrinogen to fibrin. Slowly moving erythrocytes and leukocytes become entrapped in the fibrin meshwork and a loosely adherent thrombus is formed. The thrombus may detach from its site of origin and circulate in the bloodstream (i.e., it becomes a *thromboembolus*), only to lodge when the diameter of the thrombus approximates the diameter of a blood vessel downstream. Deep vein thrombi commonly travel through the systemic venous circulation, pass through the right side of the heart, and lodge in the pulmonary circulation. When these thrombi stop circulating at the division of the main pulmonary artery into the right and left pulmonary arteries, death often occurs within minutes. This is known as *pulmonary thromboembolism*.

If the thrombus remains attached to the blood vessel wall, it becomes closely adherent to the wall of the vein within a week and increases in length by a process known as *propagation*. Secondary inflammatory changes develop. Inflammation may injure valves and cause *valvular incompetency* (i.e., when valve leaflets are injured, they cannot close completely and effective unidirectional flow of blood and emptying of veins cannot occur.) Valvular incompetency causes poor blood flow and DVT is perpetuated. The thrombus is ultimately invaded by fibroblasts that synthesize collagen, and scarring of the thrombus occurs. Endothelial cells within the thrombus proliferate and organize, resulting in neovascularization (i.e., new blood vessel formation) and partial restoration of blood flow (i.e., *recanalization*).

Diagnosis: Clinical Manifestations and Laboratory Tests

Although approximately 50% of all DVTs are asymptomatic, the remaining individuals commonly complain of swelling and pain or a dull ache in the calf or thigh, especially when walking. Since DVT is uncommon in the absence of risk factors, medical history is often significant. Patients often report a history of recent surgery, trauma, cancer, oral contraceptive use, prolonged inactivity, or heart failure. A strong family history (a minimum of two first-degree relatives) of DVT is also common and suggests a genetic susceptibility.

Physical examination of the leg may reveal some edema, deep muscle tenderness, a palpable cord (i.e., the affected vein may feel like a rope deep beneath the skin), and distension of superficial collateral veins. Patients may also demonstrate a low-grade fever, tachycardia, elevated white blood cell count, and increased erythrocyte sedimentation rate, all of which are signs of an ongoing inflammation within the affected vein (i.e., *phlebitis*).

The specific site of DVT determines the location of physical findings. Swelling in the foot and ankle with calf pain and tenderness suggest DVT in the venous sinuses of the soleus muscle and posterior tibial and peroneal veins. Pain and tenderness in the lower thigh and popliteal region suggest DVT higher up in the femoral vein. Swelling, pain, and tenderness in the entire leg indicates that thrombosis has developed in an ileofemoral vein.

There are numerous conditions that can mimic DVT, including a localized muscle strain, Achilles tendon rupture, and cellulitis. Because of the difficulty in making a precise diagnosis based on the patient's medical history and physical examination and because treatment can cause potentially serious complications, specialized tests are crucial.

Duplex ultrasonography has become the most widely used test in the initial evaluation of DVT. The procedure may be performed at the patient's bedside and is highly sensitive and specific. The examination allows direct imaging of the venous circulation while simultaneously providing information regarding blood flow (i.e., duplex). Imaging often shows a narrow vein and prominent collateral vessels. Doppler ultrasonography is used to determine the rate of blood flow through reflections of sound waves from red blood cells. Sound frequency is proportional to the velocity of blood flow. The technique is also useful in assessing the competence of venous valves. If valves have been severely damaged, retrograde blood flow (i.e., reflux) may be heard. It should be mentioned, however, that the accuracy of this test is highly dependent on the skill of the technician.

Patients in whom DVT is strongly suspected but ultrasound is equivocal are now being referred for *gadolinium-enhanced magnetic resonance venography*. This exam has a sensitivity of 100%, a specificity of 96%, and may provide some information about the age of the thrombus.

Ascending contrast venography is rarely used anymore because it is expensive, invasive, and exposes the patient to ionizing radiation. Risks of contrast media-induced allergic reactions and nephropathy (i.e., kidney injury) are also significant.

Appropriate Therapy

The objectives of treatment for DVT are to prevent extension and embolization of existing thrombi, minimize damage to venous valves, and prevent development of additional thrombi. *The standard treatment for DVT is systemic anticoagulation with heparin to a target partial thromboplastin time of 1.5–2.0 times normal*. This therapy both reduces the risk for PTE and decreases the frequency of recurrent thrombophlebitis (i.e., inflammation of the veins as a result of an intravascular blood clot) by 80%. Heparin acts as a catalyst to significantly accelerate the rate at which antithrombin III neutralizes thrombin and activated coagulation factor X. Systemic anticoagulation does not directly lyse thrombi but inhibits propagation and allows natural fibrinolysis to occur.

After therapeutic heparinization, warfarin treatment is initiated. Warfarin alters the synthesis of prothrombin and coagulation factors VII, IX, and X in the liver by interfering with the action of vitamin K. Heparin and warfarin therapies should overlap to decrease the possibility of a hypercoagulable state. Hypercoagulability may occur during the first few days of warfarin therapy because warfarin also inhibits synthesis of the natural anticoagulant proteins C and S. The recommended treatment for the first episode of uncomplicated DVT is 3–6 months of warfarin to maintain a target international normalized ratio (INR) of 2.0–3.0. After a second episode, warfarin is continued indefinitely. The risk for recurrent DVT is increased significantly in the presence of factor V Leiden mutations, antiphospholipid antibodies, and deficiencies of antithrombin III, protein C, or protein S. Lifelong anticoagulation is recommended for these conditions.

Recently, enoxaparin—a depolymerized heparin that exerts an anticoagulant effect primarily by inhibiting factor Xa—has been shown to be equally safe and effective for treatment of DVT. Because of its predictable dose–response relationship, enoxaparin does not require monitoring of its anticoagulant effect and has been promoted for outpatient treatment. Enoxaparin also has fewer adverse effects than traditional unfractionated heparin (i.e., lower risk for bleeding and osteoporosis and less inhibition of anticoagulant protein C and S synthesis).

Many studies have evaluated the efficacy of fibrinolytic (i.e., thrombolytic) agents in the treatment of DVT. Although faster clot lysis is observed with alteplase than with heparin, alteplase is not more effective in reducing the incidence of post-phlebitis syndrome. Furthermore, the risk for bleeding complications is higher. Alteplase, a recombinant DNA-derived form of human tissue-type plasminogen activator, is best used to treat ileofemoral venous thrombosis complicated by massive extremity edema and cyanosis. To be effective, however, the drug should be administered before extensive cross-linking of fibrin occurs, that is, ideally within 5 days of clot formation.

Surgical removal of the thrombus may be required in selected patients, especially when DVT is not responsive to anticoagulation, and in pregnant patients who should not be treated with thrombolytic agents or anticoagulants.

Prevention of DVT is the best form of management. There are a number of well-established, non-pharmacologic and pharmacologic measures to reduce the risk of DVT in hospitalized patients. Prevention is tailored for the patient based on risk factors. Elevation of the foot of the bed promotes venous blood flow in the legs. Slight flexion of the knees is desirable. A footboard enables the patient to perform leg exercises while in bed. Sitting in a chair for long periods following surgery should be discouraged, and early ambulation after childbirth or surgery is ideal. Compression (i.e., "support") stockings and sequential compression devices are effective in reducing the risk of calf vein thrombosis. These stockings function by increasing venous blood flow and increasing the release of endothelial fibrinolytic factors and are safe for use in almost all patients. Compression devices encircle the legs and provide alternating periods of compression to the lower leg.

Low-dose unfractionated heparin and low-molecular–weight heparin (LMWH) with enoxaparin have both been shown to significantly reduce the frequency of postoperative DVT and PTE. LMWH appears to be more effective in the orthopedic surgery patient and is associated with a lower risk for bleeding complications. Heparin products are contraindicated in patients who have recently been treated with a craniotomy or have shown signs of intracranial or gastrointestinal bleeding. Platelet count must be carefully monitored for early detection of heparin-induced thrombocytopenia (i.e., low platelet count), which occurs with peak frequency within 1 week after the initiation of treatment. Lifetime anticoagulation with low-dose warfarin is appropriate for patients with hypercoagulability or paralysis as risk factors.

Serious Complications and Prognosis

By far the most serious complication of DVT is PTE, which may be fatal. PTE occurs in nearly two thirds of patients with inadequately treated deep calf vein thrombosis. Other common, potentially serious complications include chronic venous insufficiency due to venous valve injury and varicose veins. With early and appropriate treatment, however, prognosis in most patients is good. Close follow-up of the patient is critical because recurrence of DVT is common.

Suggested Readings

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