Venous Thromboembolism and Cancer
Gregory Piazza, MD, MS

Case Presentation 1: A 64-year-old man with prostate cancer who recently underwent radical retropubic prostatectomy presented to the emergency department with sudden-onset exertional dyspnea and chest heaviness. On physical examination, he was tachycardic with a heart rate of 110 beats per minute, normotensive with a blood pressure of 100/76 mm Hg, and hypoxic with an oxygen saturation of 88% on room air. Left lower extremity edema and calf tenderness were noted. Contrast-enhanced chest computed tomography demonstrated bilateral segmental pulmonary embolism (PE) without right ventricular enlargement. A left lower extremity venous ultrasound documented left femoral, popliteal, and calf deep vein thrombosis.

Case Presentation 2: A 70-year-old woman with renal cell carcinoma underwent resection of a solitary right upper lobe metastatic pulmonary nodule and was referred to the Vascular Medicine clinic after surveillance chest computed tomography performed 1-month postoperatively demonstrated a right lobar PE. She noted fatigue since her surgery but denied any dyspnea or chest discomfort. On physical examination, her heart rate was 82 beats per minute, blood pressure was 102/66 mm Hg, and oxygenation was 96% on room air. Cardiac and pulmonary examinations were unremarkable.

Overview
Although the association between cancer and venous thromboembolism (VTE) was first noted in 1823 by Bouillard, Trousseau provided the most detailed early description in 1865. VTE is now recognized as a common cause of morbidity and mortality in patients with cancer. Increasing life expectancy attributable to advances in cancer therapy and greater use of imaging for cancer surveillance have contributed to the growing incidence of VTE in patients with malignancy. The rate of symptomatic VTE in patients with cancer who have been hospitalized approaches 5%.1 VTE, especially when unprovoked, may herald an impending diagnosis of cancer in a subset of patients without known malignancy.

Although the frequency of VTE is considered highest among patients with solid tumors, hematologic malignancies also increase the risk. Cancer-related therapies including chemotherapy and erythropoiesis-stimulating agents further increase the risk of VTE. Frequently used in a variety of cancers, vascular endothelial growth factor receptor inhibitors and epidermal growth factor receptor inhibitors have also been associated with VTE. Tamoxifen doubles the risk of VTE. Indwelling central venous catheters for the administration of chemotherapy, antibiotics, and parenteral nutrition represent a common risk factor for VTE in patients with cancer.

Validated bedside risk stratification tools such as the Khorana score2 are available to identify patients with cancer who are at a particularly high risk for VTE.

Pathophysiology
Virchow’s triad of stasis, thrombophilia, and endothelial injury plays a critical role in the pathophysiology of VTE in patients with cancer. However, a second triad comprising changes in tumor biology, coagulation activation, and inflammation further describes the pathogenesis of thrombosis in the patient with malignancy.3 Pathophysiological changes that favor thrombosis in patients with cancer include platelet activation, direct factor X activation, decreased hepatic anticoagulant synthesis, reduced hepatic clearance of coagulation factors, and autoimmune phenomena such as the development of antiphospholipid antibodies.4 Most patients with active cancer have evidence of chronic systemic coagulation activation, such as elevated plasma D-dimer levels.3
Enhanced expression of tissue factor plays a critical role in local cancer invasion, metastasis, and thrombosis (Figure 1).\textsuperscript{3} Mutations in oncogenes such as k-ras and tumor suppressor genes such as p53 lead to constitutive expression of tissue factor by cancer cells.\textsuperscript{5} In addition, tissue factor expression may be enhanced in cells of the tumor microenvironment such as fibroblasts, macrophages, and endothelial cells. Increased tissue factor expression plays a key role in angiogenesis, a necessary step in tumor growth and eventual metastatic spread.\textsuperscript{5,5} Coagulation-dependent mechanisms by which tissue factor enhances angiogenesis include increasing thrombin generation, subsequent cleavage of fibrinogen to fibrin, platelet activation, and formation of an extracellular matrix rich in platelet-derived angiogenic growth factors.\textsuperscript{3} Coagulation-independent mechanisms include tissue factor–mediated signaling via protease-activated receptors enhancing tumor cell proliferation, invasion, and angiogenesis.\textsuperscript{3} The cytoplasmic domain of tissue factor may be directly involved in increasing the expression of vascular endothelial growth factor and in the regulation of cell migration and invasion through interaction with integrins and actin-binding protein 280.\textsuperscript{3}

Increased tissue factor expression on tumor cells in patients with cancer has been associated with higher risk of VTE. In a retrospective cohort study of 122 patients with pancreatic cancer, the risk of VTE was nearly 6-fold higher in patients with increased tumor cell tissue factor expression than in those with low tumor cell tissue factor expression.\textsuperscript{6} Increased tissue factor expression also correlated with histological markers of angiogenesis supporting the role of tissue factor in tumor biology and thrombosis.

**Inflammation**

Activation of coagulation in patients with cancer promotes local and systemic inflammation that reciprocally contributes to a prothrombotic state. Thrombin and activated coagulation factors VIIa and Xa appear to modulate gene expression through protease-activated receptors, resulting in increased production of proinflammatory cytokines such as interleukin-6, interleukin-8, and interleukin-10.\textsuperscript{3} Activated platelets further enhance inflammation through increased expression of factor such as P-selectin and CD40 ligand.

Inflammatory factors promote thrombosis through enhanced expression of adhesion and procoagulant molecules on the surface of endothelial cells and monocytes.\textsuperscript{3} Expression of cytokines, including tumor necrosis factor-α and interleukin-1β, induces the expression of tissue factor on endothelial cells and downregulates the expression of thrombomodulin, favoring a prothrombotic state at the vessel wall (Figure 1).\textsuperscript{4}

**Microvascular Thrombosis**

Formation of microvascular thrombus comprising fibrin and platelets around the tumor cells (thrombus cloak) represents a critical step in metastasis (Figures 1 and 2).\textsuperscript{3} Microvascular thrombus around the tumor cell facilitates migration along the vascular endothelium and provides protection from natural killer cell–mediated immune response.\textsuperscript{3} Inhibition of the formation of microvascular thrombus in experimental models of tumor cell inoculation results in rapid clearance of cancer cells from the host microcirculation.\textsuperscript{7} The antineoplastic effect of antithrombotic and antiplatelet agents may be, at least in part, mediated by their capacity to inhibit microvascular thrombosis.

**Circulating Microparticles**

Circulating microparticles are small (0.1–1 μm) membrane vesicles with a phosphatidylserine-rich surface that are shed from platelets, erythrocytes, endothelial cells, lymphocytes, monocytes, smooth muscle cells, and cancer cells. Mutation of k-ras and inactivation of p53 are critical steps in carcinogenesis and have been closely associated with the shedding of tissue factor–bearing microparticles from cancer cells.\textsuperscript{5} Coexpression of prothrombotic proteins such as tissue factor and P-selectin glycoprotein ligand-1 on the surface of circulating microparticles promotes fibrin deposition, and matrix formation for tumor angiogenesis and platelet recruitment and aggregation, as well (Figure 3).\textsuperscript{8} Furthermore, the negatively charged
phosphatidylserine-rich surface promotes the aggregation and subsequent activation of coagulation factors.\(^8\) Complement-enriched circulating microparticles expressing Fas ligand may play a key role in cancer cell survival by suppressing the antitumor host immune response.\(^8\)

Elevated tissue factor–bearing circulating microparticle levels have been associated with an increased risk of VTE in patients with cancer.\(^9\) In a case-control study, 30 patients with cancer diagnosed with an acute VTE were compared with 60 patients who had cancer without known VTE.\(^9\) The median number of tissue factor–bearing microparticles in patients with cancer and VTE was greater than in patients with cancer without VTE. Elevated levels of tissue factor–bearing microparticles were associated with an almost 4-fold increase risk of VTE in patients with cancer. In a small randomized, controlled trial, increased numbers of tissue factor–bearing microparticles detected by impedance flow cytometry identified patients with cancer at high risk for VTE.\(^10\) Prophylactic anticoagulation with enoxaparin in a subset of these high-risk cancer patients with increased levels of tissue factor–bearing microparticles was associated with a trend toward a reduction in VTE in comparison with observation (5.6% versus 27.3%, \(P=0.06\)).

### Prognosis

The risk of recurrent VTE is 3-fold higher in patients with cancer who experience an initial venous thromboembolic event in comparison with patients who do not have cancer and develop VTE.\(^11\) Mortality after hospital discharge is nearly double among patients with cancer who subsequently developed VTE in comparison with those who do not.\(^1\) Fatal PE contributes to a high 30-day mortality in patients with active malignancy who subsequently develop VTE.\(^12\)

Incidentally diagnosed PE detected on imaging studies performed for cancer surveillance has been traditionally believed to carry a benign prognosis. However, a retrospective cohort study demonstrated no difference in the risk of recurrence and cumulative survival between patients who have cancer with symptomatic PE and those with incidentally diagnosed PE.\(^13\)

### Treatment

#### Anticoagulation

For patients with active cancer, low-molecular-weight heparin monotherapy without the transition to oral anticoagulation is preferred over warfarin by evidence-based guideline recommendations.\(^14\) In a randomized, controlled trial of 676 patients with cancer, monotherapy with the subcutaneously administered low-molecular-weight heparin dalteparin (200 IU/kg once daily for 1 month, followed by a daily dose of approximately 150 IU/kg for 5 months) was compared with oral anticoagulation with a vitamin K antagonist (target international normalized ratio, 2.5) for the prevention of recurrent thrombosis in patients who have cancer with acute, symptomatic proximal deep vein thrombosis, PE, or both.\(^15\) During the 6-month study period, 8% of patients in the dalteparin group had recurrent VTE in comparison with 15.8% of patients in the oral-anticoagulant group (hazard ratio, 0.48; \(P=0.002\)). No significant difference in bleeding was noted between the dalteparin group and the oral-anticoagulant group. A systematic review of randomized, controlled trials comparing long-term treatment with low-molecular-weight heparins versus oral anticoagulants (vitamin K antagonist or ximelagatran) in patients with cancer and symptomatic objectively confirmed VTE demonstrated a reduction in VTE (hazard ratio, 0.47; 95% confidence interval, 0.32–0.71).\(^16\) No significant difference in the rate of major bleeding was observed between low-molecular-weight heparins and oral anticoagulants (relative risk, 1.05; 95% confidence interval, 0.53–2.10).

The role of the novel oral anticoagulants in patients who have cancer with VTE has yet to be defined. Randomized, controlled trials evaluating novel oral anticoagulants for treatment of VTE have enrolled a small proportion of patients with cancer (2%–9%). The US Food and Drug Administration has approved rivaroxaban for treatment of VTE, but current labeling does not provide specific guidance for those patients with cancer.

#### Optimal Duration of Therapy

Because patients who have cancer with VTE have an increased risk of recurrent VTE, the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic Therapy for VTE Disease recommend extended-duration anticoagulant therapy over time-limited anticoagulation in patients with active
cancer, especially if the risk of bleeding is not elevated. Because patients with cancer who are receiving anticoagulation for VTE treatment have at least a 2-fold increased risk of major bleeding in comparison with patients without cancer who are receiving anticoagulant therapy for VTE, patients with cancer who are receiving extended-duration anticoagulation for secondary prevention should be monitored closely for bleeding.

Primary Prevention

Because of the increased risk of VTE in patients with cancer, especially those undergoing oncological surgery or receiving chemotherapy, thromboprophylaxis for primary prevention of VTE has been an important research and clinical practice focus. In the Enoxaparin and Cancer (ENOXACAN) II study, extended-duration (4 weeks) thromboprophylaxis with enoxaparin reduced the risk of VTE in patients undergoing laparotomy for abdominal or pelvic malignancy. The 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Prevention of VTE in Nonorthopedic Surgical Patients recommends extended duration thromboprophylaxis for patients undergoing surgery for treatment of cancer.

In a registry of 1000 adult hospitalized patients with active cancer, few (13.9%) received extended-duration pharmacological prophylaxis after hospital discharge. VTE occurred in 5.4% of hospitalized patients with active cancer over a 90-day follow-up period. The majority of hospitalized patients with cancer (63%) who developed VTE did so after hospital discharge. A systematic review evaluated randomized, controlled trials of unfractionated heparin, low-molecular-weight heparin, vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, or mechanical intervention for primary prevention in medical oncology patients. Only low-molecular-weight heparins significantly reduced the incidence of symptomatic VTE (risk ratio, 0.62; 95% confidence interval, 0.41–0.93) in comparison with placebo (number needed to treat to prevent 1 symptomatic VTE=60). Low-molecular-weight heparins were not associated with a significantly increased risk of bleeding. Despite these data, evidence-based clinical practice guidelines do not endorse prophylactic anticoagulation for primary prevention of VTE in medical oncology patients.

Case Presentation 1: The patient was immediately started on anticoagulation with a therapeutic dose low-molecular-weight heparin as monotherapy without transition to an oral vitamin K antagonist. He noted prompt resolution of his dyspnea and chest discomfort. Serial monitoring of his prostate specific antigen demonstrated no evidence of residual or recurrent prostate cancer. He discontinued anticoagulation after completing 6 months of therapy and did not experience recurrent VTE.

Case Presentation 2: The patient was initiated on anticoagulation with therapeutic dose low-molecular-weight heparin monotherapy for treatment of incidentally diagnosed PE. Chest computed tomography performed after 3 months of anticoagulation demonstrated resolution of the PE but detected additional pulmonary nodules consistent with recurrent metastatic renal cell carcinoma. Her oncologist enrolled her in a clinical trial testing a new chemotherapeutic regimen for relapsed renal cell carcinoma. She was advised to continue on low-molecular-weight heparin monotherapy as long as her cancer was active. She did not experience recurrent VTE.

Disclosures

None.

References


Venous Thromboembolism and Cancer

Gregory Piazza

Circulation. 2013;128:2614-2618
doi: 10.1161/CIRCULATIONAHA.113.002702

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/24/2614