Venous Thromboembolism and Gliomas: The Need for Increased Vigilance

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Brain tumors, particularly malignant gliomas, have a high incidence of venous thromboembolism (VTE), but current guidelines do not support primary VTE prophylaxis for ambulatory patients with brain tumors. The often subtle presentation of VTE warrants increased vigilance for early diagnosis and treatment. This article presents a case study of a patient with VTE and offers suggestions for future research.

Mrs. X, a 55-year-old woman, initially presented with a one-month history of worsening cognitive and memory deficits. Magnetic resonance imaging revealed a right frontal enhancing lesion. A craniotomy was performed, and the pathology confirmed a glioblastoma multiforme (grade IV glioma). Perioperatively, Mrs. X received intermittent pneumatic compression and was ambulating to baseline at discharge 72 hours after surgery. Her discharge medications included dexamethasone 4 mg twice daily for management of intracranial swelling. Four weeks postsurgery, Mrs. X began a six-week course of radiation therapy with concomitant temozolamide oral chemotherapy. Six weeks postsurgery, she presented with a report of occasional left leg cramps. At this time, she was walking daily and using a stationary bike three times a week. She had no erythema, edema, or localized tenderness.

Mrs. X underwent a venous ultrasound, which was positive for deep vein thrombosis. She was managed as an outpatient with 60 mg enoxaparin twice daily. Several weeks after initiation of anticoagulation, her local primary care physician changed her treatment to warfarin because of the high out-of-pocket expense for enoxaparin. Several months later, she experienced increased neurologic symptoms from both tumor progression and an intratumoral hemorrhage. Warfarin treatment for primary venous thromboembolism (VTE) in patients with cancer is associated with increased rates of recurrent VTE and bleeding complications when compared to patients without malignancy (Gerber, Grossman, & Streiff, 2006); therefore, warfarin was discontinued. The decision also was made to remain off VTE treatment since she had completed six months of therapy.

### Venous Thromboembolism

VTE includes both deep vein thrombosis and pulmonary embolism. According to Virchow’s triad, three broad categories contribute to thrombus formation: a hypercoagulable state, venous injury, and venous stasis (Lyman & Khorana, 2009). Cancer itself confers additional risks because of multiple pathophysiologic mechanisms, including increased procoagulant expression (Lyman & Khorana, 2009).

VTE is related to significant morbidity and mortality in patients with cancer. Patients with cancer have a fourfold to sevenfold increased risk of developing VTE (Streiff, 2009), a threefold increased risk of recurrent VTE, and a threefold to sixfold increased risk of major bleeding complications related to anticoagulation compared to the general population (Carrier & Lee, 2009). In addition, VTE is a leading cause of death among patients with cancer (Lyman et al., 2007), and a diagnosis of VTE can prolong hospitalization, delay cancer treatments, and increase healthcare costs (Lyman & Khorana, 2009).

Other than cancer, risk factors for VTE include patient characteristics and comorbidities similar to those found in patients without cancer. The factors include advanced age, renal or pulmonary disease, obesity, and prior history of VTE. The primary site of cancer (e.g., brain, pancreas, ovary, kidney, stomach, bladder, lung, blood), cancer diagnosis within three months, increased biomarkers (e.g., tissue factor, D-dimer, prechemotherapy leukocytes, platelets), and cancer treatments all are associated with an increased risk of VTE (Connolly & Khorana, 2010) (see Figure 1).

Patients with brain tumors (particularly gliomas, which arise from the supporting cells of the brain) have one of
the highest VTE rates of all patients with cancer, incurring a risk of 20%–30% over the course of the disease (Gerber et al., 2006; Jenkins, Schiff, Mackman, & Key, 2009). VTE may be as high as 60% when screening is done in asymptomatic patients with postoperative glioma (Perry, 2010).

Although the relationship between cancer and VTE is not completely understood, it is explained in part by the tumor mediated activation of the coagulation pathway. Tissue factor is a glycoprotein that serves as a cell surface receptor for factor VII/VIIa, the prime initiator of the coagulation cascade. Tissue factor also has been related to tumor cell growth and stimulation of tumor angiogenesis. Glial cells are rich in tissue factor and are believe to be released during neurosurgery or times of increased disease activity or progression (Perry, 2010). Vascular endothelial growth factor is overexpressed in malignant gliomas and is associated with an upregulation of tissue factor. In addition, increased levels of biomarkers associated with thrombosis, such as D-dimer, lipoprotein (a), homocysteine, and tissue plasminogen activator, may contribute to the increased risk of VTE in patients with brain tumors (Jenkins et al., 2009; Petersen, 2009).

Cancer treatments also can increase the risk of VTE. Radiation therapy is associated with VTE in some solid tumor cancers. Evidence has not been established specifically regarding increased risk for VTE in patients with gliomas receiving radiation; however, radiation often is the first-line treatment, so that risk should be addressed when assessing the patient (Jenkins et al., 2009). Chemotherapy also is considered an independent risk factor for VTE. Newer antiangiogenic agents such as bevacizumab are approved for use in recurrent malignant gliomas (Perry, 2010). Bevacizumab is a monoclonal antibody that inhibits the vascular endothelial growth factor pathways and is associated with increased arterial embolism, VTE, and bleeding (Lyman & Khorana, 2009; Perry, 2010). Corticosteroids are used commonly in patients with brain tumors to control cerebral edema postoperatively, during radiation, and during times of tumor progression. Corticosteroids can lead to increased levels of factor VII, VIII, XI, and fibrinogen levels, which can intensify an already hypercoaguable state (Gerber et al., 2006).

Figure 1. Selected Risk Factors for Cancer-Associated Thrombosis


Guidelines for Treatment and Assessment

An increased level of clinical suspicion for VTE is necessary when evaluating a patient with cancer. Evaluation should include the patient’s risk profile and assessment of subtle symptoms such as extremity heaviness or calf cramping (National Comprehensive Cancer Network [NCCN], 2011; Streiff, 2009). Classic symptoms such as pain or unilateral edema may not always be present. The Wells Criteria (NCCN, 2011), a clinical prediction model used in combination with D-dimer testing in the diagnosis of VTE, has not been validated in most patients with cancer. Patients with cancer have a threefold increase in false positive D-dimer testing; therefore, obtaining a D-dimer before diagnostic testing to assess pretest probability has limited utility (NCCN, 2011). NCCN recommends duplex venous ultrasonography for initial evaluation of a suspected deep vein thrombosis (see Figure 2). For symptoms of a possible pulmonary embolism, such as current or recent history of deep vein thrombosis, unexplained shortness of breath, chest pain, tachycardia, tachypnea, apprehension, or oxygen desaturation, computed tomography angiography is recommended (see Figure 3).

Recommendations from the American College of Chest Physicians for thromboprophylaxis in patients with cancer are limited to patients undergoing surgical procedures or who are bedridden with an acute medical illness (Hirsh, Guyatt, Albers, Harrington, & Schunemann, 2008). Neurosurgery prophylaxis includes the use of intermittent pneumatic compression perioperatively (Hirsh et al., 2008). Consensus exists among the American College of Chest Physicians and the American Society of Clinical Oncology, which recommends against the routine use of extended thromboprophylaxis for the primary prevention of VTE in patients receiving chemotherapy who are not hospitalized or bedridden (Hirsh et al., 2008; Lyman et al., 2007). To date, the only exception is patients with multiple myeloma who are receiving thalidomide or lenalidomide together with chemotherapy or dexamethasone because of the highly thrombogenic nature of those two agents (Lyman et al., 2007).

Low molecular weight heparins (LMWHs) such as dalteparin, enoxaparin, and tinzaparin are the anticoagulants of choice for the treatment of VTE in patients with cancer. Although LMWHs differ pharmacologically, limited studies have suggested similar efficacy and safety when used for the treatment of VTE (NCCN, 2011). Advantages of LMWHs include decreased risk of heparin-induced thrombocytopenia (Streiff, 2009), reduced potential for intracranial hemorrhage, superior prevention of recurrent VTE over vitamin K antagonists (Carrier & Lee, 2009), more predictable anticoagulant effect, and no need for regular coagulation monitoring (Lyman, 2009). Those benefits may offset the increased cost of LMWHs versus warfarin.
Patients with cancer should be treated for a minimum of three to six months for deep vein thrombosis and six to twelve months for pulmonary embolism (NCCN, 2011). Healthcare providers should consider extending anticoagulation indefinitely for patients with persistent risk factors or active cancer (Hirsch et al., 2008; NCCN, 2011). Dalteparin is the only LMWH approved by the U.S. Food and Drug Administration to reduce the risk of recurrence in patients with cancer who have symptomatic VTE; however, dalteparin has not been studied for a period beyond six months (Lyman et al., 2007).

**Clinical Implications and Future Research**

Advanced practice nurses have a key role in the early diagnosis and treatment of VTE. Increased vigilance and education of patients and other healthcare providers can minimize the significant morbidity and mortality associated with cancer-related VTE and subsequent treatments. With continued research, primary thromboprophylaxis with LMWH may prove to outweigh the risks and burden of VTE in ambulatory patients with gliomas or other high-risk cancers. An urgent need exists for increased research regarding the development and validation of risk assessment tools and clinical prediction rules to accurately risk stratify patients with cancer (including cancer subtypes). Additional research also is needed regarding the feasibility and cost effectiveness of

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**Figure 2. DVT Diagnosis**

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screening for VTE and elevated biomarkers such as tissue factor among patients with cancer.

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References


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