Thrombocytopenia, Deep-Vein Thrombosis, and Pulmonary Emboli in a Patient With Primary CNS Lymphoma

PATRICIA PALMER, RN, MS, AOCNS®

From University of California, Davis Health System, Sacramento, California

Author's disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Patricia Palmer, RN, MS, AOCNS®, University of California, Davis Health System, Nursing Administration, 2315 Stockton Blvd, Sacramento, CA 95817. E-mail: patricia.palmer@ucdmc.ucdavis.edu

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Primary central nervous system lymphoma is an aggressive extranodal NHL that may arise from within the brain parenchyma (90%), spinal cord, eyes, or leptomeninges in the absence of systemic involvement (Abrey, DeAngelis, & Yahalom, 1998; Zhu et al., 2009; DeAngelis & Iwamoto, 2006). Unlike other primary brain tumors, PCNSL is very chemosensitive. Historically, treatment consisted mainly of whole-brain radiation therapy (WBRT) and steroids. Over the past decade improved disease-free and overall survival have been observed with the use of high-dose methotrexate–based therapy (Batchelor et al., 2003).

Primary central nervous system lymphoma is rare, accounting for 0.5%–3% of all brain tumors and 2% of NHLs. The incidence, which is now estimated to be 0.38 per 100,000 person-years (Batchelor et al., 2003), had increased in immunocompetent and immunocompromised patients threefold over the past 30 years. This increase is noted especially in the elderly (mean age at diagnosis, 55 years). Because of the treatability of PCNSL there has been a disproportionate amount of research (40 prospective clinical trials and large institutional series published since 1978) and interest when compared to other brain tumors (Abrey et al., 2005).

The presentation is as multifocal disease in 50% of cases. The most common presenting symptoms are focal neurologic deficits (hemiparesis, dysphasia) (50%) and alterations of mental status and symptoms of increased intracranial pressure (30%). Seizure activity is less common, affecting 10% of patients. With ocular involvement, 50% of patients complain of blurred vision or visual field floaters. Primary central nervous system lymphoma (PCNSL) arising from the spinal cord will cause back and neck pain. Because PCNSL is profoundly sensitive to steroids, caution must be taken to establish a pathologic diagnosis before steroids are started (Abrey et al., 2005).

Radiologically, PCNSL lesions are isodense or hyperdense when compared to the brain on CT scan, and in most cases their enhancement is seen.

Case Study

M.F. is a 64-year-old male who presented to an outside hospital in May 2003 with chief complaints of headache, confusion, facial edema, and dysphasia. A magnetic resonance imaging (MRI) scan revealed a left frontal lobe mass. The pertinent past medical history included localized prostate cancer diagnosed 3 years prior, which was confined to the prostate and had been treated surgically. The patient also had a history of partial colectomy for a benign colonic condition 3 years prior and a history of gastroesphogeal reflux disorder. M.F. was transferred to the University Hospital, and on May 10 he had a brain biopsy and subtotal tumor resection of a deep frontal lobe mass. The biopsy was positive for a diffuse large B-cell non-Hodgkin lymphoma (NHL). A staging workup including computed tomography (CT); scans of the chest, abdomen, and pelvis and bilateral bone marrow biopsies were negative, and the diagnosis was confirmed as primary central nervous system lymphoma (PCNSL).

The patient was started on high-dose methotrexate (8 g/m^2 every 2 weeks) on May 19. On May 20 he had a single-lumen venous access port (VAP) placed. He had a rapid improvement in his memory, vocal strength, and energy. On June 17 M.F. presented for his third cycle of methotrexate; his platelet count, which had been 195,000/µL at the start of chemotherapy on May 19, was now 88,000/µL. A peripheral smear was reviewed which showed no platelet clumping, and the patient's platelet count remained in the 80,000/µL range during his 5-day hospitalization. It was decided to get a 1-week count in follow-up when the patient presented to the outpatient infusion room for his weekly VAP flush of 3 mL of 1:100 unfractionated heparin (UFH). The repeat platelet count was 134,000/µL. When the patient presented for cycle 4 of methotrexate on June 30 his platelet count was 114,000/µL and it dropped to 96,000/ during the hospitalization. The differential diagnosis for thrombocytopenia included disorders of decreased production, increased destruction, and splenic sequestration (Zeiger, 2007; Table 1).

M.F. was on a leucovorin calcium rescue (100 mg/m^2 every 6 hours) to prevent side effects from the chemotherapy. His medications were oral dexamethasone, which was being tapered (currently 4 mg daily), and oral rabeprazole (Aciphex) 20 mg daily. He was completely asymptomatic and had no evidence of bleeding or bruising. He reported mild bilateral lower extremity edema. A heparin-induced thrombocytopenia (HIT) enzyme-linked immunosorbent (ELISA) assay was drawn, as well as a Factor V mutation; his port was flushed with normal saline while the lab results were awaited.

M.F. returned for his fifth cycle of high-dose methotrexate on July 15. His platelet count on admission was 190,000/µL. He now complained of a fever of 102°F (at home) that he felt was due to a spider bite on his ear. On admission, he had the following: temperature 38.4°C, pulse 80, blood pressure 109/63, 18 respirations/min, and oxygen saturation (O_2) 96% on room air. The patient's absolute neutrophil count was 3,150/µL. Cultures were drawn and it was decided to proceed with the planned chemotherapy because the patient was not neutropenic.

During the night of the first day of admission M.F. spiked a temperature of 39.4°C. His O_2 saturation dropped to 80% but improved to 96% with movement and deep breaths. He was briefly placed on O_2 per nasal cannula at 2.0 L. M.F. was sitting up in a chair, dressed, completely asymptomatic, and without O_2 on exam the next morning. Specifically, he denied chest pain or shortness of breath, the spider bite on his ear was not secondarily infected, and he had some areas of white patches on his tongue. A spiral CT was ordered and the patient was found to have bilateral acute pulmonary emboli in the left lower lobe and right middle lobe. A Doppler study on his lower extremities showed an acute non-occluding deep-vein thrombosis (DVT) in the right popliteal vein extending into the trunk. His Factor V Leiden test was negative as was his ELISA assay for HIT. The comment on the test result suggested that if there were clinical evidence of HIT (i.e., thrombocytopenia at least 50% lower than baseline), alternative tests should be considered. A Serotonin Release Assay was ordered but it was cancelled because the send-out test was not available. The patient was placed on lepirudin, a heparin allergy was placed on his chart, and he was eventually switched to warfarin sodium upon discharge home.

On MRI the tumor is also seen as isodense or hypodense on T1- and T2-weighted images and frequently enhances. Imaging can also be affected by prior steroids. There have been subsets of patients treated on clinical trials that have been diagnosed based on MRI appearance or the tumor's response to steroids. This is problematic because there are other cranial processes that have a similar appearance and also respond to steroids (i.e., multiple sclerosis, sarcoidosis, and occasional gliomas; Abrey et al., 2005). Current thinking, however, is that biopsy conformation is necessary to establish the diagnosis.

Table 1. Thrombocytopenia: Differential Diagnosis

Decreased production (bone marrow disorder)
Aplastic anemia
Hematologic malignancies
Myelodysplastic syndrome
Megaloblastic anemia
Chronic alcoholism
Other infiltrative process, e.g., myelofibrosis, infection
Increased destruction
Immune disorders
• Idiopathic thrombocytopenic purpura
• Drug-induced, e.g., heparin, sulfonamides, thiazides, quinine
• Secondary (chronic lymphocytic leukemia, systemic lupus erythematosus)
• Posttransfusion purpura
Disseminated intravascular coagulation
Thrombotic thrombocytopenia purpura
Hemolytic uremic syndrome
Sepsis
Viral infections, AIDS
Liver failure
Preeclampsia-eclampsia
Splenic sequestration
Related diagnosis
• Idiopathic thrombocytopenic purpura
• Thrombotic thrombocytopenic purpura
• Qualitative platelet disorders
• Bleeding

Note. Adapted from Zeiger (2007).

In 2004 the International Collaborative Group Against PCNSL was formed to standardize PCNSL staging, workup, treatment, and research (Abrey et al., 2005). The management of this disease often involves neurosurgeons, neurologists, hematologists/oncologists, ophthalmologists, and radiation oncologists. Coordination and standardization is difficult because no single cooperative group has a significant representation of all of these specialties (Abrey et al., 2005; Ferreri, Batchelor, Zucca, Cavalli, & Armitage, 2003). This international group reviewed 16 published articles and 7 ongoing clinical trials for differences in staging and disease workup. Only 12/16 studies required histologic review for inclusion in the data, 2/16 allowed patients with "typical" radiographic features, 8/16 did not require a complete extent of disease evaluation to exclude systemic disease, and the systemic workup itself was variable (Abrey et al., 2005). The majority of the studies were phase II and there were no randomized phase III studies. Most investigators or cooperative groups followed similar general principles. The group concluded that additional advances and interpretation of new therapies will depend on the investigators' willingness to report data in a consistent and comparable fashion (Abrey et al., 2005).

Recommendations for baseline evaluation, staging, and workup were made by the International Collaborative Group Against PCNSL in an attempt to generate more consistent and comparable data. All patients enrolled in a clinical trial for PCNSL should have a histopathologic diagnosis, with the diagnostic procedure of choice being the stereotactic needle biopsy. There is no clinical benefit from surgical resection because of the aggressive nature of this lymphoma and the fact that the lesions are often deep-seated, which increases the risk of surgical complications. If there is suspected ocular or cerebrospinal fluid (CSF) involvement, vitrectomy or CSF cytology may help to establish the pathological diagnosis. Immunophenotyping and molecular classifications (including the basic molecular and genetic abnormalities) will help to foster future research and applications of targeted therapy (Abrey et al., 2005). Most PCNSLs (95%) are high-grade diffuse large B-cell lymphomas that express pan B-cell markers such as CD20 (Batchelor et al., 2003; Plotkin, 2005).

Clinical evaluation for baseline includes a com-

prehensive physical and neurological exam, paying particular attention to the peripheral lymph nodes and testes in older men. Also included are age and performance status (PS), the two most widely documented prognostic variables (Abrey et al., 2005); the Eastern Cooperative Oncology Group (ECOG) PS scale was used in the only prognostic model of PCNSL. A baseline evaluation of cognitive function is important both to demonstrate the benefit of therapy but also to evaluate the long-term treatment-related cognitive changes. Laboratory evaluation should include serum lactate dehydrogenase, tests of hepatic and renal function, in addition to baseline complete blood count and chemistry panel to evaluate the patient's ability to receive high-dose methotrexate.

Extent of disease evaluation is critical to the establishment of the diagnosis of PCNSL and must be done before treatment (including steroids) is started. Optimal imaging of the brain parenchyma requires a gadolinium-enhanced MRI. A contrast CT scan can be substituted in patients with contraindications or if MRI is unavailable. Lumbar puncture should be performed for CSF cytology if there is no contraindication. Cerebrospinal fluid protein is a prognostic factor and should be analyzed in all patients in addition to cell count, beta-2-microglobulin, immunoglobulin H gene rearrangement, and flow cytometry. A detailed ophthalmologic exam should be done to exclude vitreous, retinal, or optic nerve involvement.

Because occult systemic disease has been reported in up to 8% of patients initially thought to have isolated PCNSL, CT scans of the chest, abdomen, and pelvis and bone marrow biopsy are indicated (Abrey et al., 2005). The testes can be involved in older men so a testicular ultrasound should be considered. Finally, whole-body positron emission tomography (PET) scanning is being evaluated in PCNSL and may be incorporated into this evaluation (Abrey et al., 2005).

Treatment with traditional NHL regimens has been found to be ineffective secondary to the blood-brain barrier. Whole-brain radiation therapy has a history of high response rates but rapid relapse, in addition to delayed neurotoxicity, especially in elderly patients. There is ongoing controversy in the literature about the appropriate timing and use of WBRT: pre- or post-chemotherapy, or after first relapse? Since the early 1990s methotrexate-based regimens using various high doses have yielded response rates greater than 50%. Based on the Batchelor et al. regimen, the case study patient was treated with high-dose methotrexate (Table 2) for 19 cycles and is still alive with no evidence of disease 7 years later.

Each cycle of high-dose methotrexate is standardized with the use of standardized orders (Figure 1), hospital admission, prehydration with IV hydration and IV sodium bicarbonate, urine pH of 7, and urine output greater then 100 mL/h for more than 4 hours before the start of high-dose methotrexate and leucovorin calcium rescue. Leucovorin calcium acts as an antidote for methotrexate and other folic acid antagonists. Leucovorin calcium can be dosed based on measured serum methotrexate levels (Table 3)—the so-called prompt intervention in the standardized orders—or some physicians use high-dose leucovorin calcium (i.e., 50–100 mg/m^2) as rescue. Treatment toxicity of this and other similar regimens has been modest if leucovorin rescue and standardized orders are strictly followed. It is imperative that patients receive the leucovorin calcium rescue on schedule to avoid life-threatening toxicity.

In 2003, Batchelor et al. reported that after 287 cycles, 13/23 patients had no grade 3 or 4 toxicity and 12/23 experienced 18 total episodes of grade 3 or 4 toxicity (4 episodes were felt to be unrelated to methotrexate) (Batchelor et al., 2003). Mild azotemia, reversible renal insufficiency, nausea, and diarrhea were the most commonly reported side effects. Prognosis estimates are based solely on phase II data (Swinnen, 2009). Batchelor et al. reported more than 50% complete responses, with more than 25% being durable responses, using high-dose methotrexate and deferred radiotherapy (Batchelor et al., 2003).

Table 2. High-Dose Methotrexate

Induction	8 g/m^2 every 14 days until complete remission to max 8 cycles
Consolidation	8 g/m^2 every 14 days for 2 cycles
Maintenance	8 g/m^2 every 28 days for 11 cycles

USE PATIENT PLATE

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER, SACRAMENTO, CALIFORNIA

PHYSICIAN'S ORDERS AC6132-1 (1/08)

PHYSICIAN'S ORDERS FOR HIGH-DOSE METHOTREXATE (> 1 g/m^2)

DATE	**HOUR**	**Physician's Orders for HIGH-DOSE METHOTREXATE (> 1000 mg/m^2)**
Treatment date: **Cycle:**		
Height: **Weight:** **BSA:** **Allergies:**		
1. Labwork *(check all that apply)*:		
Day 1 prior to chemotherapy: CBC with auto diff, comprehensive metabolic panel (CMP)		
Daily: ☐ CBC w/ diff ☐ BMP ☐ Hepatic Panel		
2. Lab parameters for treatment:		
☐ Call MD to verify counts		
☐ Use laboratory values obtained prior to treatment (date obtained:):		
WBC ANC PLT Scr Tbili		
☐ Treat with parameters listed below:		
WBC ANC PLT Scr Tbili		
3. Hydration/urinary alkalinization:		
Start IV hydration with D5W + 150 mEq/L $NaHCO_3$ @ 250 mL/hour x 2 hours, then infuse @ mL/hour (usual 150-250 mL/hour). Once maintenance IV fluid has been running for at least 3 hours, begin checking urine pH and urine output every 2 hours. When urine pH is ≥ 7.5 for two consecutive readings AND urine output is >100 mL/hour then proceed with pre-medications and chemotherapy. Once urine pH is ≥ 7.5 continue to monitor urine pH every 4 hours until the methotrexate level is ≤ 0.05 mcM.		
DO NOT INTERRUPT OR DECREASE IV FLUID RATE DURING METHOTREXATE INFUSION		
4. Antiemetics:		
☐ Dexamethasone 10 mg IV x 1 dose 30 minutes prior to methotrexate		
☐ Ondansetron 8 mg IV x 1 dose 30 minutes prior to methotrexate		
☐ Lorazepam ☐ 0.5 mg ☐ 1 mg PO/SL/IV Q 4 hours PRN breakthrough N/V		
☐ Prochlorperazine 10 mg PO/IV Q 6 hours PRN N/V not relieved by lorazepam		
☐ Famotidine 20 mg IV x 1 dose prior to methotrexate		
ONCOLOGY PHYSICIAN'S SIGNATURE:		
PI number: **Pager number:**		
ATTENDING PHYSICIAN'S NAME/CO-SIGNATURE (if required):		
PI number: **Pager number:**		

Figure 1. UC Davis standardized orders for high-dose methotrexate.

Table 3. Dosing of Leucovorin Calcium Rescue

Methotrexate level	Leucovorin calcium dose
< 5.0×10^{-7} M	10 mg/m² q6h
5×10^{-7}–10^{-6} M	30–40 mg/m² q6h
> 5×10^{-6} M	100 mg/m² q3–6h

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an idiosyncratic immune-mediated disorder caused by the development of antibodies to platelet factor 4 (PF4) and heparin. Clinical HIT is a severely prothrombotic state seen in 1%–5% of patients receiving heparin. The finding of thrombocytopenia or a new thrombus in a patient receiving heparin or low-molecular-weight heparin (LMWH) necessitates careful assessment for HIT (Coutre, 2003; Coutre, 2010). Heparin is the most common cause of drug-induced thrombocytopenia and the most common cause of thrombocytopenia in hospitalized patients. Next to bleeding, HIT is the most significant adverse effect associated with heparin therapy.

There are two clinical forms of heparin-related thrombocytopenia. Type I, or heparin-associated thrombocytopenia (HAT), is a non–immune-mediated reaction seen in up to 30% of patients receiving heparin. It often presents early in heparin exposure (1–2 days), is asymptomatic, causing mild thrombocytopenia (platelet counts rarely < 100,000/μL), and resolves spontaneously after heparin is stopped. In contrast, type II, or HIT, is a much more severe immune-mediated reaction with serious consequences. It generally develops 5–10 days after the start of heparin, causing a greater than 50% reduction in the baseline platelet count, and predisposes patients to thrombotic complications. The diagnosis is made primarily upon clinical presentation, which can vary; HIT can occur early or late, and platelet counts can be within the reference range even after a fall of more than 50% (Zinkovsky & Antonopoulous, 2008).

HIT PATHOPHYSIOLOGY AND ETIOLOGY

Heparin is a negatively charged sulfated glycosaminoglycan with a high-binding affinity for PF4. PF4 is a positively charged, heparin-neutralizing protein contained in platelet alpha granules. PF4 is a member of the CXC subfamily of chemokines that binds to heparin and other negatively charged glycosaminoglycans with high affinity. PF4 is released with platelet activation and will bind to negatively charged glycosaminoglycans expressed on the cell surface of endothelial cells, but it will bind to heparin preferentially. The formation of the large heparin and PF4 complexes leads to the exposure of neoepitopes, which allows IgG antibodies to crosslink via their FC portion and activate the platelets. Activated platelets release prothrombotic microparticles, and cause platelet consumption and thrombocytopenia (Coutre, 2003; Coutre, 2010; Ortel, 2009; Sandset, 2010). The true cause of the thrombotic events associated with HIT is unknown. It is thought that the activated platelet aggregation and their removal from circulation leads to thrombocytopenia and thrombus. Another possible cause is that these multimolecular antibody complexes interact with monocytes, producing tissue factor and causing endothelial injury. The development of this prothrombotic state in the setting of a dropping platelet count is a relatively unique aspect of HIT that distinguishes it from other drug-induced thrombocytopenias (Coutre, 2010).

More than 12 million patients and almost one-third of all hospitalized patients receive heparin each year; HIT antibodies can be detected in up to 50% of them. These antibodies can circulate for 3 months or more in 40% of the patients. Because the diagnosis is based on both clinical and serologic grounds, clinicians should consider HIT a clinicopathologic syndrome (Warkentin, Greinacher, Koster, & Lincoff, 2008). A positive HIT antibody screen without clinical symptoms is not HIT. Conversely, patients with clinical symptoms suspicious of HIT should begin treatment prior to confirmation by laboratory testing because this testing often lags behind the diagnosis or is not available (Ortel, 2009; Zinkovsky & Antonopoulos, 2008). Of the 600,000 new cases of HIT diagnosed each year, 50% will experience complications associated with thrombosis and 90,000 will die (Zinkovsky & Antonopoulos, 2008).

HIT DIAGNOSIS

The diagnosis of HIT can be challenging due to the frequency with which patients receive UFH or LMWH, the multiple potential causes of thrombocytopenia, and the lack of readily acces-

sible laboratory testing. The diagnosis is based on a series of clinical findings and laboratory results. The clinical observation of thrombocytopenia that is otherwise unexplained and is a drop of greater than 50% from baseline with a nadir above 20,000/µL is the primary clinical criterion. The median platelet count usually is 50,000/µL to 60,000/µL. Typical timing for the development of HIT in relation to the start of heparin is thought to be 5 to 10 days in a heparin-naive individual, although thrombocytopenia may not be reached until several days later (Ortel, 2009).

In patients with prior exposure to heparin (prior to 3 months but especially in the prior 30 days), platelet counts can fall more quickly. This is called "rapid onset HIT" and is seen in 15%–20% of patients diagnosed with HIT; it is thought to represent the abrupt onset of platelet activation in patients with previously circulating heparin/PF4 antibodies. There is also a "delayed onset HIT" related to both low doses of heparin (i.e., catheter flushes) and large doses of heparin (coronary artery bypass machine). In this incidence the patient may present with thrombocytopenia or a new thrombosis days to weeks after the initiation of heparin. Other clinical manifestations include skin lesions at subcutaneous heparin injection sites and systemic reactions (i.e., fever, chills, cardiorespiratory distress).

Presentation with a new thromboembolic complication is seen in 50% of all patients with HIT. Of the patients who present with "isolated HIT" (thrombocytopenia only), 50% will develop a thromboembolic event. Venous thromboembolism is more common then arterial and pulmonary embolisms are very common. Arterial thrombosis of the lower extremities is common; strokes and myocardial infarction are less common. Two rare but well-described thromboembolic events are cerebral sinus venous thrombosis and adrenal vein thrombosis that may lead to hemorrhagic infarction of the adrenal gland (Zinkovsky & Antonopoulos, 2008).

The National Comprehensive Cancer Network and others recommend the use of diagnostic algorithms in the diagnosis of HIT. One such algorithm developed by Warkentin et al. is the 4T pretest probability score (Table 4) (NCCN, 2010; Ortel, 2009; Warkentin, Aird, & Rand, 2003).

Laboratory conformation is obtained from highly specific assays that unfortunately lag behind the clinical diagnosis. These assays are not recommended for screening in asymptomatic patients because of the frequency of circulating HIT antibodies after heparin exposure without clinical features. The two fundamental types of assays are functional (platelet activation or serotonin release assay) (SRA) and antigenic (ELISA; Table 5).

Table 4. The 4T Pretest Probability Score Algorithm

	2 Points	1 Point	0 Points
Thrombocytopenia	> 50% platelet fall to nadir ≥ 20,000	30%–50% platelet fall or nadir 10,000–19,000	< 30% platelet count fall or nadir < 10,000
Timing of onset of platelet fall (or other sequelae of heparin-induced thrombocytopenia)	Days 5–10 or ≤ day 1 if prior heparin exposure within the last 30 days	> Day 10 or timing not clear (missing platelet counts) ≤ day 1 with prior heparin exposure within the last 30–100 days	< Day 4 without recent exposure
Thrombosis or other sequelae	Confirm new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions, or suspected thrombosis (not proven)	None
O***t***her causes(s) of platelet fall	None evident	Possible	Definite

Note. A score (from 0–2) should be determined for each category above, resulting in a total potential score from 0 to 8. Pretest probability score: High 6 to 8; Intermediate 4 to 5; Low 0 to 3. Adapted with permission from Warkentin, Aird, & Rand (2003).

HIT MANAGEMENT

If the diagnosis of HIT is strongly suspected clinically, heparin must be discontinued immediately. This includes heparin-bonded catheters and heparin flushes of intravascular catheters. A heparin allergy must be placed in the patient's record and signs must be posted at bedside to prevent incidental heparin exposures. Low-molecular-weight heparin should also be avoided because of its high potential for cross-reactivity with HIT antibodies (Zinkovsky & Antonopoulos, 2008). Because the risk of thrombosis is high up to 30 days after heparin is discontinued, and because patients may be asymptomatic, the patient should initially be screened for DVT by Doppler studies and spiral CTs regardless of symptoms. If anticoagulation is indicated use of a nonheparin anticoagulant is required. The direct thrombin inhibitors (DTIs) lepirudin (Refludan) and argatroban have level 1C evidence for use in this clinical setting (Coutre, 2001; NCCN 2010; Zinkovsky & Antonopoulos, 2009). If the patient is on warfarin or another vitamin K antagonist for anticoagulation at the time of diagnosis, he or she must be reversed with either oral or IV vitamin K. Warfarin used in the setting of acute HIT antibodies (before the platelet count has recovered) can predispose patients to microvascular thrombosis (Ortel, 2009). Prophylactic platelet transfusions in patients without active bleeding are not recommended.

Lepirudin is a recombinant protein that is modified and derived from hirudin (a natural medicinal anticoagulant found in leech saliva). It is a very potent and irreversible DTI that forms a 1:1 complex with thrombin. It is not structurally similar to heparin and therefore does not cross-react with heparin, PF4, or HIT antibodies. Dosing is outlined in Table 6.

Transition to warfarin after the acute phase of HIT and after the platelet count has recovered to at least 150,000/µL is recommended. Warfarin is started with a low maintenance dose (maximum of 5 mg) without a loading dose until the INR target is reached for a minimum of 5 days. During this time the patient is bridged with a DTI. Duration of treatment should be at least 3 months for DVT and longer if clinically indicated for more serious thromboembolic events (Ortel, 2009).

WHAT ELSE COULD CAUSE THIS?

Thrombosis is a common complication in patients with cancer. It is estimated that about 20% of patients with cancer experience venous thromboembolism (VTE; Karimi & Cohan, 2010; Streiff, 2009). Surgery is estimated to increase the risk of postoperative VTE by twofold in cancer patients, and is also associated with a three- to fourfold increase in pulmonary embolism (Karimi & Cohan, 2010; Streiff, 2009). One study looking at patients who had surgery to remove a glioma found that these patients had a 70% risk of developing a VTE compared to patients who did not have surgery (Wun & White, 2009). Other risk factors for thrombosis and cancer include central venous catheters (Naina et al., 2010), immobilization, trauma, previous history of vein thrombosis, older age, prothombotic mutations such as Factor V Leiden and prothrombin 20210A, elevated D-dimer levels, elevated C-reactive protein, elevated soluble P-selectin, body mass index ≥ 35 kg/m^2, and antiphospolipid antibody syndrome (Wun & White, 2009). The thromboembolic com-

Table 5. Laboratory Confirmation of Heparin-Induced Thrombocytopenia

Assay	Type	Time to results	Specificity/sensitivity	Cost and difficulty
Platelet activation	Functional	2–3 h	Sensitivity: 30%–50%	Inexpensive; simple
Serotonin release (SRA)	Functional	Days	Sensitivity: 90%–98% Specificity: early phase 95%; late phase 80%–97%	Technically demanding; time consuming; not readily available
Enzyme-linked immunosorbent (ELISA)	Antigenic	Days	Sensitivity: 90% Specificity: early phase 95%; late phase 50%–93%	Drawback: may detect insignificant heparin-induced thrombocytopenia antibodies

Table 6. Non-Heparin Alternative for the Treatment of Heparin-Induced Thrombocytopenia

Agent	Therapeutic dose	Clearance	Half-life	Monitoring	Adverse effects
Lepirudin (Refludan)	0.4 mg/kg IV bolus (up to 110 kg), followed by 0.15 mg/kg per hour (up to 110 kg)	Renal	80 min	Measure aPTT 2 hours after initiation of therapy and after each dose adjustment Therapeutic range: 1.5 to 2.5 x baseline (optimal aPTT, < 65 sec)	Bleeding with therapeutic dose in 17.6% of patients: antibodies develop in 30% of patients

Adapted from Zinkovsky & Antonopoulous (2008).

plications of central venous catheters may be underestimated because the diagnosis may not be considered in symptomatic, but especially in asymptomatic, patients (Burns & McLaren, 2009). Finally, patients with PCNSL have an 18%–60% risk of VTE, in contrast to the 6%–7% rate seen in patients with systemic lymphoma (Gerber, Grossman, & Streiff, 2005).

Discussion

This case study illustrates the importance of being vigilant in the assessment of patients with cancer for thrombosis and drug-related complications. The patient in the case study was, for the most part, asymptomatic for all of these potentially life-threatening complications of therapy. The advanced practitioner needs to be both aware of the potential complications of cancer and therapy and an astute clinician to interpret often subtle clinical signs and symptoms. It was a fever of unknown origin coupled with a decreased O_2 saturation that led to the diagnosis of bilateral pulmonary emboli in this patient (O'Connell et al., 2006).

This case occurred in 2003 before there were published guidelines and algorithms by the NCCN and others. The diagnosis of HIT was made more from the clinical presentation and was not confirmed by the ELISA test. The documentation of thrombocytopenia was outside the window of 5–10 days from the start of heparin. However, because the patient's platelet count was not continually monitored, it is impossible to know when the reductions actually happened. Day 10 from the initiation of heparin would have been May 29; his platelet count was 245,000/µL on May 23 and the next recorded platelet count was 184,000/µL on June 4. This could represent the start of HIT, and the resulting thrombocytopenia actually happened between June 4 and June 16, when it was first noted. Also, in 2003 the gold standard (SRA) was very difficult to obtain; by the time it was ordered it may have been too late in the course of HIT to be helpful.

Using both the HIT Pre-Test Probability Score Assessment and the NCCN guidelines, the appropriate tests would have been ordered in the early phase of suspected HIT as M.F.'s score would have been a 5. Furthermore, the guidelines recommend four extremity duplex ultrasounds to identify subclinical DVT, which would have likely found his asymptomatic DVT and interventions may have prevented the bilateral pulmonary embolisms that subsequently developed. These guidelines are very important in preventing what could be devastating thrombotic complications: 10%–20% lose a limb and 20%–30% die (Zinkovsky & Antonopoulos, 2008).

With the use of heparin being so common in hospitalized patients it is important for the advanced practitioner to recognize the potential for this severe immunologic reaction. HIT is more common than most perceive it to be, and therefore, it can easily be missed (Zinkovsky & Antonopoulos, 2008). The thrombocytopenia encountered with the diagnosis of HIT differs from other drug-induced thrombocytopenias in a number of ways: thrombocytopenia may not be as severe and occurs in a well-defined time frame related to the start of heparin, patient typically do not bleed, and a non-heparin anticoagulant is essential for treatment because of a significant thrombotic risk (Ortel, 2009). The diagnosis is made primarily upon clinical presentation, which can vary and is often confounded by other medical conditions. This presents unique chal-

lenges to the advanced practitioner caring for cancer patients receiving heparin.

DISCLOSURE

The author has no conflicts of interest to disclose.

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