Thrombosis and Coagulation Abnormalities Associated with Cancer

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ABSTRACT

Abnormalities of hemostasis and malignancy have been recognized since the 19th century. Thrombosis and hypercoagulability are reported in as many as 60 percent of patients with malignancies. Decreased levels of protein coagulation factors, circulating anticoagulants and platelet numbers, and function changes are reported. The purpose of this work is to report a case of portal thrombosis in a patient with a myeloproliferative disorder and to review protein coagulation and platelet abnormalities associated with malignancies. The clinical laboratory assessment of these abnormalities is reviewed. The patient was a 59-year-old woman who was referred to the Vanderbilt University Medical Center with a diagnosis of septic portal vein thrombosis. After evaluation, it turned out that she had a myeloproliferative disorder and portal vein thrombosis secondary to that. Hypercoagulative states have been reported with a variety of carcinomas and other neoplasms. They may or may not be associated with acquired or genetic deficiencies of antithrombin III, protein C and/or S. Factors I, V, VIII:C, IX, and XI have all been reported as being elevated and implicated in hypercoagulability in patients with neoplasms. Increased platelet turnover and decreased survival have been noted in patients with disseminated tumors. Thromboses with lysis of the thrombus may be monitored by increased levels of fibrin degradation products, D-dimer, fibrinopeptides A and B, and platelet factor IV among others. There are frequently decreases in coagulation inhibitors including antithrombin III, protein C and protein S. These changes lead to a state of low-grade disseminated intravascular coagulopathy where thrombus formation is a more frequent occurrence than is hemorrhage. Treatment for the malignancy, for instance radiation and/or chemotherapy, can have an adverse effect on the hemostasis activity. Among the malignancies associated with abnormalities of hemostasis are mucinous adenocarcinomas and some myeloproliferative disorders. In summary, abnormalities of hemostasis can be a presenting aspect of a variety of malignancies. The diagnosis and therapy of the underlying malignant disorder often has to consider an associated hemostatic abnormality.

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Introduction

Trousseau in 1865 is given credit as the first to describe clearly abnormalities of hemostasis in patients with cancer. Alterations of coagulation and malignancy were described by others in the 1930s and subsequently. These aberrations are varied and complex. Many malignant diseases have been associated with either hyper- or hypocoagulability. The malignancies include carcinomas of the liver, lung, breast, kidney, sarcomas, melanomas, lymphocytic and myeloproliferative disorders. Thrombotic episodes occur in up to 60 percent of patients with mucin secreting adenocarcinomas, myeloproliferative disorders, acute promyelocytic leukemia, and brain tumors.2,8

The objectives of this paper are to: (1) present a brief patient history of a woman with a myeloproliferative disorder and thromboses; (2) review protein coagulation and platelet abnormalities associated with malignancies; and (3) emphasize the laboratory diagnosis and follow-up particularly of patients with malignant disorders and thromboses.

Case Report

This is a 59-year-old white woman who was referred to Vanderbilt University Medical Center (VUMC) with a diagnosis of septic portal vein thrombosis. Over the past five to six weeks, she had experienced episodes of sharp chest pains not associated with activity, but they occasionally radiated down the left arm. Ten days prior to admission, she had dull crushing substernal chest pain that was not relieved by nitroglycerine. Evaluation by electrocardiogram, chest x-ray, and history and physical exam, were essentially normal at that time. Right upper quadrant abdominal tenderness remained. Subsequent radiologic and ultrasound studies identified a partial portal vein occlusion presumably owing to thrombosis. She was admitted for anticoagulation therapy consisting of heparin and subsequently coumarin. Elevation of the alanine transaminase 75 IU/L (reference range 4 to 40 IU/L), aspartate transaminase at 107 IU/L (reference range 4 to 40 IU/L) and alkaline phosphatase at 132 IU/L (reference range 40 to 110 IU/L) were noted. After anticoagulation, the patient was sent home only to return to the hospital two days later. She was now febrile with a temperature of 102.1°F. Antibiotics were begun. Her prothrombin time was prolonged. There was a slight elevation of her white cells. Packed cell volume was 0.41 and platelets were 141,000 mm³. Radiologic studies identified a complete portal vein thrombosis. There was evidence of hepatosplenomegaly. No evidence of other abdominal varices or gastrointestinal problems were noted.

Past medical history was noncontributory. The patient had been on premarin for approximately three months for an elevated cholesterol and osteoporosis.

Pertinent laboratory findings: Fibrinogen was 620 mg/dl (reference range 190 to 400 mg/dl). Fibrin split products were 1.256 (reference range less than 1:4). Prothrombin time (PT) and partial thromboplastin time (PTT) values—levels of antithrombin III, protein S, and protein C were all determined to be within the reference ranges. A bone marrow biopsy was obtained which revealed a moderately hypercellular marrow with the presence of megakaryocytes, atypical megakaryocytes and was considered to be suggestive of a myeloproliferative disorder. Subsequent bone marrow evaluations revealed a myeloproliferative disorder not otherwise classified.

Discussion

Hypercoagulability in Malignancies

Hypercoagulable states have been reported with a variety of carcinomas and other neoplasms. Often these are associated with acquired or genetic deficiencies in antithrombin III, protein C, and protein S. These abnormalities have been associated with portal vein thrombosis.3,9 A variety of conditions have been reported to lead to portal vein thrombosis (table I). The patient presented here had normal values for antithrombin III, protein S, and protein C. The use of the estrogen compound in her therapy is a known risk factor for venous thrombosis and has been reported to be associated with a 2.3 fold increase in risk for patients receiving it. Estrogen use has been reported to be associated with hepatic vein thrombosis (HVT) in patients with myeloproliferative disorders that are either overt or latent. The HVT has been reported in 10 of 18 cases in one study.1 This prompts suggestion that patients who have sus-
TABLE I

Conditions Associated with Portal Vein Thrombosis

**Specific**
- Cirrhosis
- Neoplasm
  - Pancreatic carcinoma
  - Hepatocellular carcinoma
- Infection
- Inflammatory
  - Pancreatitis
- Myeloproliferative disorders
- Idiopathic

**Non-specific**
- Hypercoagulable states
  - Congenital
    - AT—III deficiency
    - Protein C deficiency
    - Protein S deficiency
  - Acquired
    - Pregnancy
    - Oral estrogen intake
    - Circulating lupus anticoagulant
- Diseases
  - Inflammatory bowel diseases
  - Systemic lupus erythematus
  - Behcet's disease
  - Scleroderma
  - Idiopathic pulmonary hypertension
  - Paroxysmal nocturnal hemoglobinuria
- Other Conditions
  - Noncirrhotic portal fibrosis
    - Idiopathic fibrosis/hypertension
    - Hepatoportal sclerosis
  - Blunt trauma
  - Abdominal surgery
  - Splenectomy in patients with myeloproliferative disorders
  - Distal splenorenal shunt surgery
  - Liver transplantation
  - Transhepatic obliteration of varices

Expected neoplasms, particularly myeloproliferative disorders and hepatic vein thrombosis, not be given estrogen.

Neoplastic disorders associated with hypercoagulable states have been reported with increased numbers of platelets or dysfunctional platelets. The platelet count in this patient was slightly below the lower limit of our reference range. It is probable that this lower platelet count was secondary to consumption in the hepatic vein thrombosis. Although no evidence is shown of activation of plasminogen, tissue activating factors or circulating anticoagulants, this patient did have a positive test for fibrin split products. Fibrin split products are an indication of ongoing thrombosis with attempts at fibrinolysis. Increased fibrinogen, fibrin split products, D-dimer, fibrinopeptide A and B, cryofibrinogens, fibrin monomer, B-beta 15-42 and related peptides, platelet factor 4, and beta-thromboglobulin may be noted. Altered fibronectin and antithrombin levels are seen in many individuals with disseminated malignancy. Mucinous adenocarcinomas are frequently associated with thrombus formation. The sialic acid moiety of secreted mucin initiates coagulation by the nonenzymatic activation of Factor X to Factor Xa. In pancreatic carcinoma, systemic trypsin triggers intravascular coagulation events. The neoplasms most frequently associated with disseminated intravascular coagulation (DIC) include myeloproliferative and gastrointestinal cancers (table II).

TABLE II

Malignancies Associated with Disseminated Intravascular Coagulation

<table>
<thead>
<tr>
<th>Maligancies</th>
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<tbody>
<tr>
<td>Acute promyelocytic leukemia</td>
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<tr>
<td>Acute myelomonocytic leukemia</td>
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<tr>
<td>Lymphomas (immunoblastic)</td>
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<tr>
<td>Hodgkins disease</td>
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<tr>
<td>Biliary cancer</td>
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<tr>
<td>Breast cancer</td>
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<td>Colon cancer</td>
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<td>Gastric cancer</td>
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<tr>
<td>Lung cancer</td>
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<tr>
<td>Malignant melanoma</td>
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<td>Ovarian cancer</td>
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Patients with neoplasms can have a range of clinical laboratory findings related to low grade DIC (table III). In a series published in 1991 by Wehmeier et al, of 260 patients with myeloproliferative disorders, 33 were first recognized and a diagnosis of myeloproliferative disorder established because of bleeding or thrombotic events.\(^\text{10}\) It was also noted in this group of patients that thrombotic events were less frequent in patients below the age of 40. Overall thrombohe­morrhagic events were observed in 48 percent of patients with chronic myelo­proliferative disorders.\(^\text{11}\) This patient’s bone marrow was characterized by mega­karyocytic abnormal forms. Thrombosis is noted as a major complication in poly­cythemia vera, essential thrombocythe­mia and acute promyelocytic leukemia.\(^\text{4}\)

**HYPOCOAGULABILITY**

Hypocoagulability is usually the result of the thrombotic episodes. Although there have been reports of circulating anticoagulants and fibrinolytic activities in myeloproliferative disorders, hypoco­agulable states are more frequently associated with B lymphocyte malignancies. Multiple myeloma has been reported to be associated with 15 percent to 60 percent of the patients having hemorrhagic complications. Up to 60 percent of patients with IgM Myeloma or Walden­strom’s macroglobulinemia have been reported as having hemorrhagic compli­cations.\(^\text{5}\) Acquired von Willebrand’s syndrome occurs in situations in which the quantity or the function of the von Wille­brand glycoprotein is diminished.

Normally, von Willebrand factor (vWF) in plasma complexes and stabilizes factor VIII. The vWF is also important in the interaction between endothelium and platelets. An acquired form of von Wille­brand disease (vWD) has been reported with multiple myeloma, Walden­strom’s macro­globulinemia, monoclonal gam­mopathies, hairy cell leukemia, chronic lymphocytic leukemia, and malignant lymphomas.\(^\text{6}\) Platelet dysfunction and subsequent bleeding is a frequent com­plication of paraprotein anemias and mono­clonal gammopathies. Screening tests that will allow for the detection of the vWD include the bleeding time, the FVIII:C, FVIII:vWF, and the FVIII:RCoF. The FVIII:C inhibitors can be demonstrated by mixing patient plasma with normal plasma. A normal prothrombin time and thrombin time are expected. Clinically, these may present with mucosal bleeding. Acquired vWD patients are often elderly with no history of bleeding or have no family history for coagulopa­thies.\(^\text{6}\)

Circulating anticoagulants to factor VIII and abnormalities in the conversion of fibrinogen to fibrin have also been reported. Acquired deficiencies of factor X and IX, as well as V, plasminogen, antithrombin III, proteins C and S, and alpha subunit 2–plasminogen inhibitors
have been reported. The presence of lupus anticoagulants have been reported in Hodgkin's and non-Hodgkin's lymphomas. As a clinical entity to be evaluated, it should be noted that one report indicated that 8 of 29 patients with the lupus anticoagulant without clinical evidence of systemic lupus erythematosus had a malignant diagnosis in the final outcome.\footnote{7}

Screening tests, such as the activated and non-activated partial thromboplastin times, the prothrombin time and the bleeding times for coagulation are not good predictors of thrombosis in patients.\footnote{7} These observations are consistent with the patient presented here.

**Conclusion**

Malignancies, particularly myeloproliferative disorders, are known to be associated with a variety of thrombohemorrhagic phenomena. The cause of this can be abnormalities in platelet numbers and/or function, abnormalities in a variety of protein coagulation factors, the presence of procoagulants being made by the tumor or interrelated factors. The laboratory and the attending physician should be alert to consider an underlying malignancy in a patient who presents with thrombosis and/or a hemorrhagic disorder particularly after the age of 40.

**References**