Hemostatic Abnormalities Associated with Cancer and Its Therapy*†

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ABSTRACT

Hemostatic abnormalities associated with malignancy have been described since the middle of the 19th century. Abnormalities associated with hypercoagulability and hemorrhage are reported in various percentages of patients depending upon the underlying neoplasm and the type of therapy. Changes in the quantitative and qualitative aspects of protein coagulation factors, anticoagulant proteins, circulating anticoagulants, platelets, and vascular responses have been noted. Clinical or subclinical disseminated intravascular coagulopathy (DIC) and associated paradoxical bleeding are common. Hemorrhage may be associated with a decrease of particular coagulation factors or alterations of vascular integrity and platelet numbers or function in various combinations.

Evaluation of hemostatic abnormalities associated with cancer (HAAC) includes a careful history and physical examination, assessment of the prothrombin and activated partial thromboplastin times, platelet count, a test for fibrin or fibrinogen degradation products, and assay of fibrinogen levels. Specific findings may suggest the need for tests for naturally occurring protein anticoagulants (e.g., protein S, protein C, and antithrombin III), coagulation inhibitors, abnormalities of the fibrinolytic system, or other esoteric tests. Testing for F1 + 2 and fibrinopeptide A may be useful in determining early activation of prothrombin and thrombin, respectively, and a clue to incipient onset of DIC.

Besides the disease, therapies for cancer can alter hemostatic activity. Chemotherapy has been reported to be associated with venous and arterial thromboses, cerebrovascular events, and coagulopathies. Radiation therapy decreases platelet production, particularly if the active bone marrow has been included in the field. Laboratory evaluation of HAAC requires consideration of the type of malignant disorder, the history and physical condition of the patient and any therapy.

Introduction

Trousseau's syndrome of migratory venous thrombosis was first described in a case report in the 1860s. This patient was found to have a carcinoma of the gastrointestinal tract. Since then, other coagulation abnormalities have

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been reported in cancer patients. Adenocarcinomas were most often associated with hemostatic abnormalities associated with cancer (HAAC) in the early history, but since then episodes of thrombosis have been reported in more than 90 percent of patients with acute promyelocytic leukemia. Other myeloproliferative disorders, mucinous adenocarcinomas, and brain tumors have been reported with up to 90 percent incidence of thrombosis. Hemorrhage has also been reported, especially with B-cell abnormalities. Significant bleeding has been reported in 15 to 60 percent in the patients with a variety of myelomas and Waldenstrom’s macroglobulinemia.

Purpose

Objectives of this review are to: (1) describe abnormalities of hemostasis associated with a variety of cancers; (2) explore the role of chemotherapy in the etiology of HAAC; (3) discuss the appropriate tests and a diagnostic sequence useful in the identification of HAAC; and (4) identify cost effective tests.

Methods to Identify HAAC

Methods used to identify HAAC include: (1) the history and physical and assessments of vascular integrity; (2) platelet number and function; (3) protein procoagulant and anticoagulant factors; (4) acquired circulating anticoagulants; and (5) abnormalities of fibrinolytic activity. Methods for coagulation testing include: (1) activated partial thromboplastin time and prothrombin time; (2) fibrinogen assay; (3) thrombin time; (4) specific factor assays; (5) assays for protein anticoagulation factors; (6) fibrin degradation products; (7) assessment of fibrinolysis; (8) platelet testing; and (9) a search for acquired circulating anticoagulants.

Results of Testing in HAAC

Platelets

Platelet abnormalities of number as well as function have been described. Tumor replacement of the bone marrow decreases the number of platelets. It has also been hypothesized that circulating cytokines reduce platelet numbers by down-regulating platelet stem cells. Abnormal platelet function has been described as part of the myeloproliferative process. Hemorrhagic diatheses have been reported in many of the immunoglobulin-producing neoplasms. These abnormal immunoglobulins result in altered platelet aggregation, decreased platelet factor III, and other abnormalities of platelet performance. Neoplasms that produce IgM cause these alterations with greater frequency than those that produce IgG.

The clinical manifestations include ecchymoses, epistaxis, intraoperative hemorrhage, altered platelet aggregometry studies, and an increased bleeding time. Laboratory diagnosis of platelet antibodies presents challenges, although assessing immunoglobulin presence on the platelet surface may be useful. Bleeding times are variable, and the lack of reproducibility limits their usefulness. Attention should be directed at the underlying disease. Plasmapheresis may be helpful in the therapy of the hemostatic disorder, particularly in instances of platelet antibody production. Platelet component therapy can be in the form of single-donor or pooled random platelet units.

Protein Coagulation Factors

Increases or decreases of the protein coagulation factors of fibrinogen (I), factor (VIII), and others have all been reported to occur, as have changes in circulating heparin-like anticoagulants. Fibrinogen levels can be measured directly by an immunoassay or indirectly through thrombin time. Factor VIII assays are available in most laboratories. The presence of Factor VIII inhibitors as a potential cause of bleeding should be considered. Specific coagulation abnormalities may be caused by excess circulating anticoagulants or by destruction of the capacity to produce protein anticoagulation factors. In rare instances, circulating heparin-like anticoagulants have been reported, particularly in patients with multiple myeloma.
Antithromboplastin activity and increased antithrombin have been noted. Although antithrombin can be measured in most laboratories through a commercially available assay for antithrombin III, it may not be offered in smaller laboratories. Assays of antithromboplastin activity are beyond the scope of most clinical laboratories. Therapy for these disorders has generally been disappointing, but the choices include administration of appropriate blood components, factor replacement, or heparin as indicated.

Paradoxically, the presence of so-called lupus-like anticoagulants results in increased thrombosis. Patients with an acquired lupus anticoagulant may present with unusual thrombosis of the upper and/or lower extremity deep veins and pulmonary emboli. Immunoassays for lupus-anticoagulants, which are actually antiphospholipid antibodies, are available. Treatment for the coagulopathy includes heparin and coumadin therapy. The underlying disorder must also be treated.

Cancer patients may also have hereditary abnormalities of protein coagulation factors as a coexisting disorder. A recently described factor V gene mutation may exist in 5 to 10 percent of the population. This defect is associated with a 10- to 50-fold increase in thrombosis, depending upon whether the patient is hetero- or homozygous. Other less common hereditary causes of thrombosis that may complicate cancer are deficiencies of proteins S and C.

### Changes in Hemostatic Factors Associated with Cancer Treatment

Several chemotherapeutic agents used in the treatment of cancer have been reported to alter hemostasis. These include melphalan, which is most often associated with thrombocytopenia, and doxorubicin, reported to be associated with enhanced fibrinolysis and thrombocytopenia. Methotrexate has been associated with thrombocytopenia, enhanced anticoagulant activity, and liver toxicity. The enhanced anticoagulant activity may be related to the liver toxicity of this agent. Tamoxifen, used in the treatment of carcinoma of the breast, has been associated with decreased antithrombin III levels, which can lead to thrombosis.

Actinomycin-D has been associated with a decrease in vitamin K-dependent coagulation proteins, so that one may see abnormalities in the prothrombin time and the partial thromboplastin time secondary to decreases in Factors II, VII, IX, and X. Bleomycin is associated with vascular endothelial damage, which leads to complications of thrombotic microangiopathy and platelet injury. Vincristine has been associated with platelet qualitative changes and von Willebrand factor as well as vascular phenomena such as peripheral vasospasm (Raynaud's syndrome), especially when used in association with cisplatin. Cisplatin has, rarely, been associated with thrombotic microangiopathy. Fluorouracil has been associated with increased von Willebrand antigen, increased adenosine diphosphate (ADP) platelet aggregation, and thrombocytopenia. Several reports of the use of chemotherapeutic agents in combination have indicated that there is between a 5 percent and almost 20 percent incidence of thromboembolism associated with multidrug therapy.

The mechanism of thrombosis related to chemotherapy is possibly threefold, including: (1) cytolysis with release of procoagulants; (2) hepatocytotoxicity with decreased protein C and protein S; and (3) altered vascular endothelium resulting in platelet activation. The therapeutic approach to the coagulation disorder is complicated since the patient suffers hemostatic abnormalities because of therapy for the underlying cancer. Replacement with appropriate blood components and anticoagulation therapy are usually indicated.

### Discussion

A variety of visceral adenocarcinomas and myeloproliferative disorders are associated with abnormalities of hemostasis. These include disseminated intravascular coagulation (DIC), thrombocytopenia, abnormalities of
fibrinogen, thrombotic microangiopathy, circulating inhibitors, and alterations of protein anticoagulant factors in various combinations. In effect, any and all aspects that relate to the hemostatic mechanism can be altered by the underlying malignancy or related therapy.

The manifestations of coagulation abnormalities and malignancy can include changes in the peripheral blood differential, such as schistocytosis, increased reticulocytes, and increased leukocytes. The fibrinogen may be borderline or normal, clotting factors may be altered or normal, and there may be elevation of fibrin degradation products. The cost-effective laboratory approach to making the diagnosis should use those tests that are commonly available, readily run in the clinical laboratory, and clinically indicated. Tests for fibrin degradation products, review of the peripheral smear for signs of DIC and/or thrombotic microangiopathy, protein coagulation cascade testing, platelet counting and function, and factor assays may be useful. However, there are no effective laboratory means for measuring abnormalities of vascular integrity or function. Elevated fibrinopeptide A released from fibrinogen reflects in vivo thrombin activity. Cleavage of prothrombin can be assessed by the F 1 + 2 test which measures prothrombin fragments 1 + 2. Plasma levels of fibrin D-dimers may be useful in assessing fibrin deposition and have been linked to fibrin in expanding tumors. Platelet counts must be evaluated critically as the number of platelets may be normal but their function abnormal, or the number can be decreased but function fairly normally. Screening tests such as the activated partial thromboplastin time, prothrombin time, and bleeding times are not good predictors of thrombosis in patients with cancer.

The suspicion of an underlying carcinoma should be high in any patient over the age of 40 that presents with a circulating inhibitor or deep venous thrombosis. In one report, 8 of 29 patients with a lupus anticoagulant without clinical evidence of systemic lupus erythematosus had a malignancy when a definitive diagnosis was eventually made.

Conclusion

Thrombohemorrhagic abnormalities are associated with a variety of cancers. The clinical laboratory can provide information through the peripheral smear (looking for evidence of microangiopathic hemolytic anemia as a result of underlying DIC), alteration in platelet numbers and/or function, abnormalities in a variety of protein coagulation factors, and the presence of inhibitors and fibrinogen and fibrin breakdown products. Chemotherapy or radiation therapy for patients with cancer results in additional changes to the hemostatic balance. The laboratory can not contribute significantly to the diagnosis of abnormalities owing to alterations in vascular integrity or function except to look indirectly for changes that might be associated with angiopathy. A good history and physical examination and a high index of suspicion for the potential of an underlying malignant disorder when an elderly patient presents with a hemostatic abnormality are essential. Treatment should be for the neoplasm and, where indicated, appropriate blood components and/or anticoagulants. The HAAC are a challenge to the clinician and the laboratory to make a timely diagnosis and apply appropriate therapy. Thrombosis and/or hemorrhage in the cancer patient should be evaluated in light of the original diagnosis and the effects of any therapy which has been used.

References


