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Commentary

Platelet Number and Platelet Function: Their Importance in Hemostasis

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(A COMMENT ON: BARBUI T, CORTELAZZO S, VIERO P, BASSAN R, OINI E, SEMERARO N. Thrombohaemorrhagic complications in 101 cases of myeloproliferative disorders: relationship to platelet number and function. *Eur J Cancer Clin Oncol* 1983, **19**, 1593–1599.)

THE PLATELET has a central role in the initial phase of blood coagulation. In the event of blood vessel injury, the exposed subendothelium stimulates platelet adhesion with subsequent platelet degranulation and release of platelet aggregating substances such as adenosine diphosphate (ADP). Circulating platelets are thus recruited to the nascent blood clot, with further platelet degranulation and platelet aggregation. Simultaneous with this platelet activation, thrombin is generated by activation of the circulating coagulation proteins. Thrombin stimulates platelets in addition to its activity in the conversion of fibrogen to fibrin, with concurrent stabilization of the blood clot. This coagulation process may go awry at a number of levels, including deficiencies or abnormalities in the platelets.

Thrombocytopenia is caused by decreased platelet production or increased platelet destruction. In patients with cancer, thrombocytopenia may be due to myelophthisis or to chemotherapy or radiotherapy. Thrombocytopenia due to increased platelet destruction is also seen in cancer patients. Disseminated intravascular coagulation may be found in patients with solid tumors, particularly those of gastrointestinal origin. Clinically, a major problem in these patients is a 'hypercoagulable' state with increased clotting tendencies. Acute promyelocytic leukemia is commonly accompanied by thrombocytopenia and disseminated intravascular coagulation; bleeding is a major complication in this setting. A more common cause of thrombocytopenia due to increased platelet destruction in the general population is idiopathic thrombocytopenic purpura (ITP). In this disease the thrombocytopenia is caused by the interaction of platelets with specific anti-platelet antibodies or immune complexes, and the rapid uptake of these 'coated' platelets by the reticuloendothelial system. In the older patient with ITP an underlying malignancy such as lymphoma or, more uncommonly, a solid tumor should be considered [1].

Thrombocytosis, paradoxically, may also be associated with bleeding. Reactive thrombocytosis is found in patients with inflammatory disease, with gastrointestinal bleeding and with malignancy, and is not associated with undue bleeding. The thrombocytosis which accompanies the myeloproliferative diseases (polycythemia vera, idiopathic myelofibrosis, essential thrombocythemia and chronic myelocytic leukemia) is due to uncontrolled marrow proliferation and clonal expansion of megakaryocytes [2]. Although thrombosis is a clinical problem in the myeloproliferative diseases, particularly polycythemia vera, bleeding is also a major manifestation of these diseases [3]. The abnormal hemostasis in the myeloproliferative diseases is due not only to thrombocytosis but also to abnormal platelet function, even in those patients with normal platelet counts.

The function of platelets is important to consider in all patients with a history of excessive

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bleeding. If such a patient has a normal platelet count and a normal screening coagulation study, tests of platelet function should be considered. The bleeding time remains one of the best tests of platelet function. An abnormal bleeding time may reflect a rare congenital platelet disorder associated either with abnormalities in the platelet membrane glycoproteins (e.g. Glanzman's thrombasthenia) or with abnormalities of content or secretion of intracellular platelet granules (e.g. congenital storage pool disease). Prolongation of the bleeding time is a hallmark of von Willebrand's disease, a disease of the Factor VIII molecule and its interaction with the platelet. In the more common acquired platelet dysfunction caused by aspirin the bleeding time may also be prolonged, and there is recent evidence to suggest that alcohol may further magnify this prolongation of the bleeding time with aspirin [4]. Prolongation of the bleeding time may be found in the myeloproliferative syndromes, whether the platelet count is elevated or normal.

Platelet aggregometry is useful in evaluating the patient with a suspected defect in platelet function. The thrombasthenic platelets will respond poorly to the standard aggregating agents (ADP, epinephrine, collagen). In storage-pool disease, congenital or acquired by aspirin ingestion, the second wave of aggregation, which reflects the release of intracellular granular contents, is usually absent. In classic von Willebrand's disease the platelets fail to aggregate in response to the antibiotic, ristocetin. In the myeloproliferative disorders the most common defect is failure to aggregate in response to epinephrine, a finding associated with deficiency of α-adrenergic receptors [5].

Dr. Barbui and colleagues in the *European Journal of Cancer and Clinical Oncology* have demonstrated convincingly that the abnormal aggregation patterns as well as abnormalities in other tests of platelet function do not correlate with the clinical hemostatic disorder in patients with myeloproliferative disease. What recommendations can be made for the management of patients with myeloproliferative disease to prevent the hemostatic complications? The group at highest risk in the paper by Barbui *et al.* are patients with polycythemia vera: 18 of the 21 thrombohemorrhagic events occurred in the polycythemia patients and all these patients had thrombocytosis. These data and data presented by the Polycythemia Vera Study Group suggest that in patients with polycythemia vera the hematocrit should be maintained under 45% and the platelet count under 500,000/μl. Alkylating agents should be used with great caution because of their leukemogenic effects. Radioactive phosphorus may be less leukemogenic [6]. Phlebotomy combined with hydroxyurea is currently an accepted method of management. In the other myeloproliferative diseases it is less clear that the thrombocytosis requires therapy. A small group of patients with myeloproliferative disease suffer micro-occlusive vascular disease with pain or even gangrene of the digits associated with thrombocytosis. These patients do benefit from lowering the platelet count. Anti-platelet drugs such as aspirin should be used with caution in patients with myeloproliferative disease. Whereas aspirin even in very low doses may be useful in patients with micro-occlusive disease, the routine use of aspirin in myeloproliferative disease is fraught with the hazards of excessive bleeding of gastrointestinal origin [7].

Clinical trials of therapeutic approaches to patients with myeloproliferative disease as well as continued laboratory investigation of the myeloproliferative megakaryocyte and platelet are necessary to provide more definitive answers to the difficult questions of optimal evaluation and hemostatic complications in management of patients with myeloproliferative disease.

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