Immune Thrombocytopenia (ITP): An Historical Perspective

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In 1735, two young girls presented to the German physician Paul Gottlieb Werlhof with symptoms of epistaxis and purpura. One young patient had a spontaneous remission, while the second suffered from repeated relapses. Describing these cases in his “Disquisitio medica et philologica de variolis et anthracibus,” Werlhof named the disorder “Morbus haemorrhagicus maculosus.” Mueller-Eckhart in his historical review of immune thrombocytopenic purpura (ITP) found that Brohm and Kraus (1883) and Denys (1883) independently were the first to report the relationship between thrombocytopenia and the clinical syndrome described by Werlhof. A controversy soon emerged regarding the pathologic mechanisms responsible for the thrombocytopenia. Frank (1915) proposed that “Die Essentielle Thrombopenia” resulted from toxic suppression of the megakaryocyte by a substance produced in the spleen. A year later, Kaznelson, a Viennese medical student, reported on the beneficial effect of splenectomy in this disorder. However, in contrast to Frank, he proposed that thrombocytopenia resulted from increased platelet destruction in the spleen. Over the next 30 years, little evidence emerged to support either theory. In 1946, Dameshek and Miller studied bone marrow from patients with ITP and found an increase in the total number of megakaryocytes in the bone specimens, but the majority of cells appeared not to be producing platelets. Effective platelet production appeared to increase after splenectomy.

A series of reports published in 1951 firmly documented an immunologic role for accelerated platelet destruction. Evans and co-workers reported an association between Coombs test–positive hemolytic anemia and ITP, suggesting an autoimmune mechanism for thrombocytopenia. In the same year, Harrington and Moore clearly demonstrated that a humoral factor was responsible for the rapid clearance of platelets in this disorder. With these publications, “idiopathic” thrombocytopenic purpura became “immune” thrombocytopenic purpura. Subsequent studies by a number of investigators confirmed that the “humoral anti-platelet factor” was an antibody directed against platelet glycoproteins.

The dogma of ITP as a disorder exclusively due to accelerated platelet destruction was challenged again in the 1980s by investigators at the Puget Sound Blood Center. By using platelet kinetic studies with indium-111–labeled autologous platelets, these investigators found not only evidence of increased platelet clearance, but also impaired platelet production. These studies were initially viewed with a good deal of skepticism; however, additional studies performed in the last decade have demonstrated inhibition of in vitro megakaryocyte growth and maturation by antibodies from ITP patients. In addition, more recent studies have strongly supported an important role for the thymic lymphocyte in the initiation, progression, and response to treatment in ITP.

The recognition that a number of other medical conditions can be associated with the development of thrombocytopenia that is clinically indistinguishable from classic ITP has led to a separation of the disease into primary (idiopathic) and secondary forms. There is increasing recognition that the secondary forms of ITP, such as observed with the recent reports of Helicobacter pylori–associated disease, may be more common than primary disease. Our greater understanding of the complexity of the syndrome of ITP has lead to new and promising therapies such as the thrombopoietin receptor agonists and improved outcomes for the affected patients.

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