blood

Introduction to a series of reviews on clinical platelet disorders

In the 21st century, many of the exciting advances in understanding platelet function have had to do with the roles these anucleate cellular elements play in processes other than their well-known activities as agents that prevent hemorrhage and maintain vascular integrity or induce thrombosis. Platelets have now been shown to have roles in immunity, including antimicrobial defense,[1] and in cancer growth and metastasis,[2-4] tumor angiogenesis,[5] lymphangiogenesis,[3,6] inflammatory diseases,[7-9] wound healing,[10] liver regeneration,[11] and neurodegeneration.[12] Despite these numerous and varied roles of platelets in mammalian physiology and pathology, disorders of platelet number or function in general manifest most clearly as either bleeding or thrombosis. And alongside the progress in understanding the new roles of platelets in human physiology, research has also served to better elucidate the pathophysiology of clinical platelet disorders, whereas novel and improved therapies have altered their natural history. Several of these disorders are covered in the following review series:

Clinical updates in adult immune thrombocytopenia (Michele P. Lambert and Terry B. Gernsheimer [Children's Hospital of Philadelphia and University of Washington, respectively])
Thrombotic thrombocytopenic purpura (Bérangère S. Joly, Paul Coppo, and Agnès Veyradier [Hôpitaux de Paris])
HUS and atypical HUS (T. Sakari Jokiranta [University of Helsinki])
None of the above: thrombotic microangiopathy beyond TTP and HUS (Camila Masias, Sumithira Vasu, and Spero R. Cataland [Ohio State University])
Heparin-induced thrombocytopenia (Gowthami M. Arepally [Duke University])
Hematopoietic transcription factor mutations: important players in inherited platelet defects (Natthapol Songdej and A. Koneti Rao [Temple University])

All these disorders involve platelets, but the role of platelets as the primary effectors of disease pathophysiology differs among them. In immune thrombocytopenia (ITP), for example, virtually the entire clinical syndrome can be attributed to the destruction or clearance of platelets and the resulting thrombocytopenia. In contrast, some of the thrombotic microangiopathies (with the clear exception of thrombotic thrombocytopenic purpura [TTP]) are driven primarily by injury to the endothelium, either from activation of the complement system or from the toxic effects of drugs or other agents. Similarly, heparin-induced thrombocytopenia, characterized and diagnosed on the basis of the effect of heparin/platelet factor 4/immunoglobulin complexes on platelets, has thrombosis as its most serious adverse effect, and recent evidence suggests this complication may be more a result of the effect of the immune complexes on monocytes than a result of their effect on platelets.[13] Almost all the disorders display thrombocytopenia, with the exception of some of the inherited platelet defects, in which the platelet counts can be normal and the defect is purely functional.

In their update on adult ITP, Lambert and Gernsheimer discuss recent findings on the pathophysiology, diagnosis, and treatment of ITP. Their discussion of therapy emphasizes new thinking on first- and second-line therapies, high-dose corticosteroid treatment, rituximab, and thrombopoietin receptor agonists. The authors also discuss ITP in special circumstances, particularly pregnancy, and offer advice on its management.

Three articles in the series deal with thrombotic microangiopathies: TTP, hemolytic-uremic syndrome (HUS), and other thrombotic microangiopathies not primarily a result of ADAMTS13 deficiency or complement activation. Joly et al review recent findings on the pathophysiology, management, and treatment of TTP. Exciting new therapies include rituximab for autoantibody suppression, *N*-acetylcysteine, bortezomib, and agents such as caplacizumab that interfere with the platelet–von Willebrand factor interaction. In addition, these authors examine various aspects and controversies in TTP diagnosis and discuss the features and management of TTP associated with other conditions, such as pregnancy, autoimmune disease, HIV infection, and cancer. Jokiranta reviews HUS in its typical form associated with Shiga toxin-producing *Escherichia coli* infection, HUS associated with other infections, and the atypical form (aHUS) associated with inherited mutations of complement regulatory factors. Finally, Masias et al examine TTP-like thrombotic microangiopathies. These syndromes that feature thrombocytopenia and microangiopathic hemolytic anemia have a variety of causes, but they have in common widespread endothelial damage and usually do not respond to plasma exchange therapy.

In the next review, Arepally discusses heparin-induced thrombocytopenia. She describes recent evidence that heparin/platelet factor 4/immunoglobulin complexes not only cause thrombocytopenia by stimulating the platelet Fc receptor FcγRIIa but also interact with Fc receptors on monocytes and induce the synthesis of tissue factor, contributing to the prothrombotic tendency associated with this disorder. Arepally also discusses clinical scoring systems that attempt to predict which patients will develop thrombosis and the latest advances in diagnostic testing and treatment.

The review by Songdej and Rao deviates somewhat from the other articles in this series, in that the platelet disorders are inherited, rather than being acquired. In the past, the most highly studied congenital platelet disorders have been those in which mutations cause defects in proteins necessary for normal platelet function or structure, disorders such as Bernard-Soulier syndrome or Glanzmann thrombasthenia. Recently, several inherited disorders of platelet function have been found to be caused by mutations of transcription factors. Some syndromes involve transcription factors that are only active in hematopoietic cells; others affect transcription factors that also control gene transcription in other tissues. Sometimes blood cell defects dominate the features of the disorder, such as in X-linked thrombocytopenia with β-thalassemia caused by mutations of *GATA1*. In other cases, the platelet defect may represent only 1 part of a constellation of abnormalities, such as in Jacobsen syndrome, caused by hemizygous deletion of the distal tip of the long arm of chromosome 11, a region that contains the *FLI1* gene, which encodes a transcription factor that regulates a

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number of megakaryocyte/platelet genes. These and other rare disorders are reviewed in this article.

In summary, this compendium of articles provides an up-to-date examination of several clinical platelet disorders that often baffle and perplex clinicians because of their difficulty in diagnosis or complexity in therapy. These articles should go a long way toward making the disorders easier to understand and treat.

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