blood® Editorial

Introduction to a review series on rare systemic hematologic disorders

Hematology represents a diverse array of disorders, some of which are rarely encountered by practicing clinicians. To compound the dilemma, there can be wide variability of manifestations between patients within each disorder. These rare entities pose a unique challenge, because biological and therapeutic progress is based on observations made on small patient cohorts. In this series, we highlight recent insights in diagnosis and treatment of 6 rare systemic disorders that are at the border between nonmalignant and malignant disease: 3 systemic histiocytic disorders, 2 lymphoproliferative syndromes, and systemic mastocytosis. The series includes the following review articles:

- "Erdheim-Chester disease" by Julien Haroche, Fleur Cohen-Aubart, and Zahir Amoura
- "Langerhans cell histiocytosis" by Carlos Rodriguez-Galindo and Carl E. Allen
- "Pediatric hemophagocytic lymphohistiocytosis" by Scott W. Canna and Rebecca A. Marsh
- "Pathobiology and treatment of lymphomatoid granulomatosis, a rare EBV-driven disorder" by Christopher Melani, Elaine S. Jaffe, and Wyndham H. Wilson
- "Overview of Castleman disease" by Angela Dispenzieri and David C. Fajgenbaum
- "New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis" by Andreas Reiter, Tracy I. George, and Jason Gotlib

Although these diseases are widely disparate in presentation and natural history, recent progress on them owes much to the insights provided by modern "omic" technologies. Detection of somatic mutations through genomic analysis has enabled the identification of clonal disorders with potential targeted therapies in Erdheim-Chester disease, Langerhans cell histiocytosis, and systemic mastocytosis. Castleman disease has benefited from proteomic analysis to elucidate pathways for novel therapy.

Pediatric hemophagocytic lymphohistiocytosis (HLH) and lymphomatoid granulomatosis have provided important insights into dysregulation of the immune response. In pediatric HLH, failure of immune competence leads to unbridled immune activation and end organ damage, because of specific constitutional mutations crippling signaling and feedback at the immunologic synapse or because of acquired immune incompetence secondary to infection, malignancy, or underlying autoimmune activation. Similarly, lymphomatoid granulomatosis is associated with a specific pattern of immune incompetence that results in a failure to control Epstein-Barr virus infection.

We hope that this series will provide useful insights into the current understanding of these rare diseases, which are often difficult to recognize, diagnose, and treat effectively.

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