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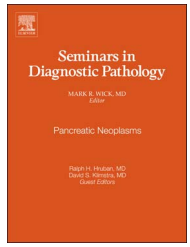

Histiocytic proliferations

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ABSTRACT

The study of Histiocytic lesions has been a passion of Pepper Dehner over the years. He has contributed several case series and reviews on various categories of these diseases for over 4 decades, with his earliest articles in the 1970s. He has written on all aspects of the disease including seminal articles on Langerhans cell histiocytosis (LCH) and their prognostic features, his experiences with regressing atypical histiocytosis, his encounters with malignant histiocytosis, and classic articles on juvenile xanthogranuloma. His contributions in the form of chapters in his 2 editions of the unique Pediatric Pathology textbook are no less important than his many articles. His experience with these lesions is highlighted in the 2 editions of the book, and the author and the audience is left wishing for more in a more current version. This article is more of a journey from descriptions and understanding of these various histiocytic syndromes to the current understanding and classifications with molecular inputs and recent advances. This article is dedicated to a master Clinician, Pathologist, and mentor whose contributions to the field of Pediatric Pathology makes him deserve beyond all doubt the title of "Father of Modern Pediatric Pathology."

The mononuclear phagocytic system

The mononuclear phagocytic system is derived from committed hematopoietic stem cells located in the bone marrow.[1–3] The 3 major components of the MPS system are the monocytes, macrophages, and dendritic cells. The term histiocyte was originally used to describe fully differentiated cells of the monocyte/macrophage lineage, but is now considered to be a descriptive term for monocytes/macrophages as well as for dendritic cells.[1] The cells of the monocyte/macrophage system are now known to be derived from myeloid stem cells that can differentiate into monocytes, interstitial dendritic cells, Langerhans cells, Veiled cells, interdigitating dendritic cells, and plasmacytoid dendritic cells. A subset of dendritic cells is also derived from mesenchymal stem cells and includes the follicular dendritic cells and fibroblastic reticulum cells.[1,3–5] While substantial advances have been made in the understanding of the MPS, an association with the immune system with a role in immunodeficiency states was suggested by Pepper with his colleagues in 1981 when they studied their experience with histiocytic disorders and found associated defects in thymus and thymic-dependent lymphocytes.[6] A brief introduction to the cells involved in the MPS and histiocytic syndromes follows.

Monocytes are circulating blood cells and populate the bone marrow and spleen, but they do not have the capacity to proliferate (differentiated cells). They serve as immune effector cells and migrate to tissues in pathologic states such as infection as part of the immune response. They are characterized by a phenotype of CD14+, CD11c+, CD68+, CD1a, and Langerin negative cells.

Macrophages, on the other hand, are resident cells in tissues and play a central role in defense against foreign

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Table 1 – Clinicopathologic classifications of histiocytosis. (Adapted with permission from Dehner.[10])

Differentiated histiocytosis
Unifocal histiocytosis and eosinophilic granuloma (bone, lymph node, and lung)
Multifocal unisystem histiocytosis (bone and lung)
Multifocal and multisystem histiocytosis (Hand–Schuller–Christian disease)
Intermediate histiocytosis (infantile histiocytosis and Letterer–Siwe disease)
Malignant histiocytosis
Malignant histiocytosis and infantile type with features of Letterer–Siwe disease
Malignant histiocytosis without erythrophagocytosis
Malignant histiocytosis with erythrophagocytosis (histiocytic medullary reticulosis of Scott and Robb–Smith)

stimuli. They too can induce cytokines and are important in control of infectious and noxious stimuli and help clean up the debris following tissue damage. They have a primary role in the control of infectious diseases. In states where they are unable to process and kill the infectious organisms they take on an epithelioid phenotype, a characteristic of all granulomatous diseases, infectious, immune or genetic, as in chronic granulomatous disease. They have a phenotype of CD14+, CD11c+, CD68+, CD163+, CD1a−, and Langerin negative cells. The epithelioid cells on the other hand show low expressions of CD14, CD68, and CD163, but have a strong reaction for lysozyme. They are an important component of the histiocytic disorders as alluded to later.[1,4,7]

Dendritic cells are unique in that they can be derived from both bone marrow myeloid precursor cells as well as from mesenchymal derived stem cells.[1,2,8] They are responsible for antigen-processing and presentation and form an important constituent of all lymphoid tissue in the body. They regulate T-cell responses to injury, and as mentioned above are of different types. They, as a group, are negative for CD14, which distinguishes them from monocyte/macrophages. Langerhans cells, which represent the major group of DC, are resident cells in skin and mucosal sites. They characteristically have cell processes in the resting phase, and upon activation can migrate to lymph nodes and to the dermis. They are capable of undergoing clonal proliferation and are responsible for the group of diseases in the spectrum of Langerhans cell histiocytosis. They are characteristically S100+, CD1a+, Langerin positive, CD163−, and CD14−. This is in contrast to the dermal dendritic cells which are usually S100−, CD1a−, Langerin−, CD68+, and Factor XIIIa positive, and represent the group of interstitial DC. Veiled cells have a similar phenotype as Langerhans cells and are thought to be a precursor form of LC, not involved in antigen presentation. Interdigitating DC are again CD1a and Langerin negative and S100+. Plasmacytic DC are a distinct subset of myeloid derived DC. They are more closely associated with monocytes and are possibly involved in plasmacytoid dendritic cell neoplasms. They show a phenotype of CD68+ and CD123+ cells that lack S100, CD1a and fascin.[7–9]

Follicular DC and fibroblast reticulum cells are stromal stem cell-derived DCs and are thought to be closer to myofibroblasts. Follicular DCs are characteristically present in the germinal follicles of lymphoid tissue and show the characteristic phenotype of CD21+, CD23+, CD35+, and fascin+ with variable staining for S100. The fibroblast reticulum cell is probably a myofibroblast and shows smooth muscle actin and sometimes keratin expression.

Nosology and classification of histiocytic disorders

The original classification of histiocytic disorders was suggested by Rappaport in 1966. Dehner suggested a categorization of histiocytic disorders into the following 3 groups: differentiated, intermediate, and malignant histiocytosis (Table 1), and also introduced a classification for familial and other histiocytic disorders (Table 2).[10] The knowledge of histiocytic disorders evolved through the next decade or so and in the second edition of his comprehensive book, Pepper suggested revision into the now accepted norm of Langerhans' cell histiocytosis and non-Langerhans' cell histiocytosis, which includes reactive lesions, inborn errors of metabolism, and malignant disorders (Table 3).[11] The group of non-LCH was similar to that described earlier (Table 2). These 2 broad major groups have remained the same over the years and continue to form the basis for the current WHO classification. Favara et al.[12] were the first to provide a unifying classification of histiocytic disorders. They grouped LCH with other dendritic cell lesions and separated them from the macrophage-related disorders. Similarly, they also divided the malignant disorders into the sub-groups of monocyte-related lesions and dendritic cell-related malignancies. This group was also the first to understand the need to recognize histiocytes as a group of immune cells that included macrophages and dendritic cells. There was further understanding of the various non-LCH lesions that led Weitzman and Jaffe to justify subdivision of this broad group of lesions into juvenile xanthogranuloma (JXG)-like and non-JXG like lesions (Table 4).[13] In a recent review article, the Histiocyte group has proposed a more encompassing classification of histiocytic disorders with the use of prognostic and novel genetic defects.[9] The broad groups remain the same, but are now grouped into 5 groups: The “L” or Langerhans' group; The “C” group of non-LCH lesions; the “R” group of Rosai–Dorfman diseases; the “M” group of malignant histiocytosis; and the “H” group that includes the hemophagocytic syndromes. This grouping will be discussed further in the description of the individual diseases.