Comment on Emile et al, page 2672

The histiocytoses: as easy as ABC (or LCMRH)

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In this issue of Blood, Emile et al, representing the Histiocyte Society (HS), have proposed a revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell (DC) lineages, taking into account recent insights regarding cell of origin, molecular genetics, and clinical features.1 For pathologists and clinicians, even those with special expertise in hematologic diseases, reactive and neoplastic proliferations of cells in the histiocytic, monocyte/macrophage, and DC lineages can be tremendously difficult to diagnose. Because many of the entities that comprise this collection of diseases are extremely rare, the combined experience of a number of institutions is useful to clinicians and others interested in the histiocytoses. This has been done before, notably by the Working Group of the HS in 1987.2 But a new perspective on these diseases would be desirable, in particular one that takes into account the advances in our knowledge of the pathology, clinical presentation, and molecular genetic features of these entities that have occurred in recent years. This is admirably accomplished by Emile et al in their article, which represents the efforts of members of the HS, which includes researchers at 26 different institutions from Europe and North America. They categorize the entities into 5 groups, designated L (Langerhans), C (cutaneous and mucocutaneous), M (malignant), R (Rosai-Dorfman), and H (hemophagocytic) (see figure). Some of the numerous insights and recommendations from the article are summarized, particularly those that relate to recent breakthroughs.

The L group includes Langerhans cell (LC) histiocytosis (LCH) and Erdheim-Chester disease (ECD), entities with similar immunophenotypes (~20% of cases of ECD have LC lesions) having recently been shown to have mutations in the MAPK pathway in >80% of cases. BRAF p.V600E mutations, identified in ~50% of cases of LCH and ECD, result in constitutive activation of the MAPK pathway.3,4 Mutations in MAP2K1 (MEK1), another component of the MAPK pathway, are identified in ~19% of LCH, including BRAF mutation–negative cases.5 The authors recommend BRAF and MAP2K1 analysis to confirm difficult cases of LCH and ECD and in patients who fail first-line treatment.

The C group, which consists of entities with a predominance of skin/mucosal involvement, is an adaptation of the 2005 classification of Weitzman and Jaffe, taking into account immunophenotypic and clinical features.6 In their discussion of the M group, the authors correctly observe that a major problem for diagnosticians is the absence of specific criteria indicative of malignancy in histiocytes. They therefore recommend that the diagnosis

<table>
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<th>Group</th>
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| L     | Langerhans cell histiocytosis (LCH)  
|       | Indeterminate cell histiocytosis  
|       | Erdheim-Chester disease (ECD)  
|       | Mixed ECD and LCH |
| C     | Cutaneous non-LCH histiocytoses  
|       | Cutaneous non-LCH histiocytoses with a major systemic component |
| M     | Primary malignant histiocytosis  
|       | Secondary malignant histiocytosis |
| R     | Familial Rosai-Dorfman disease (RDD)  
|       | Classical (nodal) RDD  
|       | Extranodal RDD  
|       | Neoplasia-associated RDD  
|       | Immune disease–associated RDD  
|       | Other non-C, non-L, non-M, and non-H histiocytoses |
| H     | Primary HLH: Mendelian-inherited conditions leading to HLH  
|       | Secondary HLH (apparently non-Mendelian HLH)  
|       | HLH of unknown/uncertain origin |

Summary of entities comprising the L, C, M, R, and H groups in the revised classification of Emile et al for the HS. Professional illustration by Patrick Lane, ScEYEnce Studios.
of malignant histiocytosis (MH) should be reserved for those patients with rapidly progressing tumors. The recent identification of frequent chromosomal gains and losses in MH, in contrast to LCH, which usually is karyotypically normal and has <5 somatic mutations, points to the potential usefulness of molecular genetic techniques in resolving difficult cases. Secondary proliferations of malignant histocytes have been identified in association with other hematologic malignancies. In some cases, a clonal relationship to the primary malignancy has been established using immunoglobulin gene rearrangement studies, BRAF mutational analysis, or another translocation or chromosomal abnormality between the primary and secondary malignancies.

The R group, which consists in large part of Rosai-Dorfman disease, is usually straightforward diagnostically because of the characteristic cytomorphic and immunophenotypic properties of the histiocytes. However, caution should be exercised in central nervous system disease, in which the clinical and radiographic appearance can simulate meningioma, and in cases with large numbers of IgG4+ plasma cells, in which IgG4-related disease must be excluded.

Entities included in the H (hemophagocytic lymphohistiocytosis [HLH]) group share the common clinical features of uncontrolled immune activation including fever, cytopenia, hepatosplenomegaly, and hyperferritinemia. Primary HLH is related to known inherited immune disorders with dysregulation of the inflammasome. Secondary HLH may be associated or triggered by an infection, connective tissue disorder, or malignancy. Interestingly, some cases of secondary HLH have recently been associated with mutations which impair cytosis, potentially blurring the distinction between primary and secondary HLH.

In summary, the authors and the HS are to be commended for their efforts to synthesize the ~100 categories of histiocytic disorders into a useful, informative, and up-to-date classification schema that includes practical recommendations for the diagnostician and the results of recent research in the field. And sometimes, the answers reveal more questions.

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**Comment on Hyvärinen et al, page 2701**

**Sweeteners for factor H**

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In this issue of *Blood*, Hyvärinen et al1 show that mutant forms of complement factor H, which are commonly associated with atypical hemolytic uremic syndrome (aHUS), have impairments in binding to sialic acid on C3b-coated erythrocytes, platelets, and endothelial cells. The findings have implications in our understanding of the mechanisms underlying aHUS and the design of therapies for complement-mediated syndromes, infections, and cancer.

The complement system is a component of innate immunity, designed to eliminate invading pathogens while sparing healthy host cells. The alternative pathway of complement is constitutively active, continuously generating small amounts of C3b, an opsonin and key component of the C3bBb C3 convertase that is necessary for amplification and progression of the complement cascade. C3b binds indiscriminately to surfaces, whether they belong to pathogens or host cells. Thus, regulatory mechanisms that distinguish self vs nonself are required to prevent complement activation on healthy cells and unwanted tissue damage.

Factor H is an important negative regulator of complement that binds to C3b and host cell surfaces, where it competes with formation of the C3bBb convertase, accelerates its decay, and provides cofactor activity for C3b inactivation. Factor H mutations are the most common genetic cause of aHUS,2 a thrombotic microangiopathy with microvascular endothelial damage, hemolysis, thrombocytopenia, and renal dysfunction. Mutations of factor H are also linked to age-related macular degeneration and C3 glomerulopathies. Furthermore, host-derived factor H can be recruited by some pathogens and tumor cells to evade immune destruction. Thus, understanding how factor H interacts with C3b and the cell surface, and distinguishes self from nonself, has clinical relevance.

Factor H is an abundant plasma glycoprotein that comprises a string of 20 short consensus domains, complement control protein (CCP) repeats,1 that interact with C3b and cell surfaces. The current model holds that CCP1-4 binds to C3b and is necessary for cofactor and decay acceleration of C3bBb. CCP19-20 also binds to C3b but possesses recognition sites for polyanion-mediated binding to the cell surface. The majority of aHUS-associated factor H mutations are clustered in CCP19-20. Polyanions, such as glycosaminoglycans,
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