**Histiocytes and Histiocytosis**

**To the Editor:**

Several points in Cline's recent review on histiocytes and histiocytosis syndromes provoke commentary from those of us who are heavily involved in the study of these perplexing disorders.

The assertion that ordinary macrophages, or "professional phagocytes" and dendritic cells share the CD1a surface antigen demeans the value of this marker in distinguishing ordinary macrophages from certain dendritic cells that are key players in lesions of Langerhans cell histiocytosis (LCH). The marker, CD1a, effectively discriminates certain dendritic antigen-presenting histiocytes from ordinary macrophages and it identifies the lesional cells of LCH, the most significant of the histiocytosis syndromes. CD1a-positive interdigitating dendritic cells and indeterminate cells (dermal Langerhans cell precursors) are featured only in exceedingly rare histiocytosis syndromes. A minority of cases of Rosai-Dorfman disease manifest CD1a-positive lesional cells, but the precise nature of the histiocyte in this disorder is still unclear. For practical purposes, histiocytes that bear the CD1a surface antigen can be presumed to be either Langerhans cells or closely related interdigitating or indeterminate dendritic cells or the pathologic counterparts of these histiocytes. They are not ordinary macrophages.

Cline's limited commentary on the relationship of LCH to hematologic malignancies like leukemia and lymphoma is misleading. Leukemia, particularly acute lymphoblastic leukemia, and lymphoma may antedate the onset of LCH, both disorders may be diagnosed concurrently or, as stated, a hematologic malignancy can develop after LCH is diagnosed and treated. Clearly treatment-induced malignancy cannot be implicated in the first two scenarios and, as Cline indicates, the contribution of therapy to the occurrence of leukemia or lymphoma in patients treated for LCH is difficult to evaluate.

The most disconcerting aspect of Cline's review is presented as a note added in proof and concerns monoclonality in the histiocytosis syndromes. The reports of Willman et al do, indeed, provide evidence that all forms of LCH are monoclonal disorders. Cline indicated that this "means that eosinophilic granuloma and relapsing Langerhans cell histiocytosis should be classified among the malignant disorders of histiocytes." An alternative view questions the meaning of monoclonality in a disorder (solitary eosinophilic granuloma of bone being the best example) that clearly lacks features of malignancy in the eyes of clinician and pathologist alike. This alternative reaction to clonality data will, in my opinion, ultimately help avoid excessive treatment of benign histiocytic disorders and lead to work designed to attain a better understanding of these perplexing diseases. Treatment of a solitary monoclonal LCH lesion (e.g., eosinophilic granuloma of bone) as a malignancy could be a serious mistake.

As a consultant pathologist and review pathologist for the Histiocyte Society, I have the privilege of seeing material from over 50 cases of the various histiocytosis syndromes (most are LCH) annually. I am unconvinced of evidence of malignancy in all but the rarest of cases and these have usually been interdigitating dendritic cell malignancies. It is ill-advised to assume that LCH, the major disorder among the histiocytosis syndromes, is malignant neoplasia on the basis of closeness when further work on basic pathogenesis is still to be done.

The results of work by Kannourakis provides evidence of an unusual cytokine profile produced by Vβ restricted T lymphocytes in lesions of LCH and calls for further inquiry into the role of nonconventional antigens and nonconventional antigen processing in the pathogenesis of LCH.

Cline's review of this very difficult field of hematology/hematopathology convincingly illustrates that the histiocytosis syndromes remain a mystifying group of disorders. The interested reader is referred to the supplemental volume of the British Journal of Cancer for an indepth review of LCH.

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**REFERENCES**


**Response**

Dr Favara makes three comments about the review "Histiocytes and Histiocytosis," published in Blood in November of 1994. The first concerns the use of the CD1a antigen to identify cells of the Langerhans/dendritic lineage and to distinguish these cells from differentiated macrophages. I have no disagreement with Dr Favara on this point. Langerhans cells have strong CD1a antigen reactivity and macrophages have relatively weak reactivity. I had thought that this point had been made both in the text and in Table 1 of the review in which cell surface and cytoplasmic markers are discussed. The review notes that Langerhans cells "present antigen in conjunction with their rich array of surface MHC class II and CD1a antigens," and the Table makes the distinction in CD1a reactivity between macrophages and Langerhans cells on a semiquantitative 0 to + scale. However, if I failed to note this distinction sufficiently clearly in the original review, then the reader should be aware that the CD1a antigen is a useful marker of Langerhans cells and reflects a surface protein that is important in their biologic function.

Dr Favara's second comment is concerned with the relationship between Langerhans cell histiocytosis and the development of leukemia. The development of leukemia after the first clinical manifestations of histiocytosis is well documented, and indeed one of my own cases cited in the review (reference 106) developed leukemia many years after the onset of histiocytosis. In this case, as in others reported in the literature, the contribution of drug therapy to leukemogenesis...
is difficult to evaluate. However, the development of leukemia before or concurrent with the manifestations of histiocytosis is more problematic. I have been unable to find a wholly satisfying case history in the medical literature to substantiate this phenomenon, although the review does cite some relevant literature (reference 46). Nevertheless, I do agree with Dr Favara that histiocytosis and leukemia are sometimes closely related processes. Indeed, in the initial version of the review article I included a case from my own records that I believe documented an early progression from histiocytosis to leukemia. However, the details and photographs documenting the progression were expunged from the final draft at the request of a reviewer who felt that they were not appropriate to a review article.

Dr Favara’s last comment concerns monoclonality in the histiocytic syndromes and relates to a note added in proof to the review. The note describes a recent publication, which, in my view, provides the most important insight into the biology of histiocytosis that has appeared in the past 2 decades. The publication clearly shows that several histiocytic disorders, ranging from eosinophilic granuloma of bone to clinically aggressive diseases, are all monoclonal in nature. Dr Favara, with a nice turn of phrase, correctly notes that eosinophilic granuloma of bone “lacks features of malignancy in the eyes of the clinician and pathologist alike.” Few would disagree with this observation. However, other histiocytic disorders such as that described by Letterer and Siwe have many of the characteristics of an aggressive malignancy. Therefore, the major issues relate to the significance of monoclonality in the origin and evolution of these histiocytic diseases and to an operational definition of malignancy—issues which must be given serious consideration in the light of the Willman publication.

Although advanced cancers are often oligoclonal as a result of accumulating molecular defects, malignant diseases are presumed to start out as monoclonal disorders. However, there are monoclonal diseases that are not malignant either in “the eyes of the clinician or the pathologist.” Benign monoclonal gammopathy, some cases of cold agglutinin disease and at least some adenomatous polyps of the colon come to mind as examples of monoclonal disorders that are not malignant. However, in each of these disorders some cases will eventuate in unambiguous malignant disease, probably as a result of accumulation of additional molecular lesions. This phenomenon has been best defined for adenomatous polyps and carcinoma of the colon.3 Therefore, in some cases the initial monoclonal disorder may be considered to be a premalignant condition. It is reasonable to ask whether some of the monoclonal histiocytic disorders fit into this category. They are disorders of cell proliferation and, as Dr Favara has noted, some appear to progress to leukemia. However, until the molecular abnormalities are defined, it may be best simply to characterize these histiocytic disorders as monoclonal and clinically benign.

In view of this new information about monoclonality, I would suggest a modification of the classification that I originally proposed (Table 1). No doubt it will be further modified as new information becomes available in the future.

Martin J. Cline
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REFERENCES

Table 1. Proposed Classification of the Histiocytic Diseases

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Macrophage</td>
<td></td>
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<tr>
<td>M-I. Macrophage storage diseases</td>
<td>Gaucher’s disease, Niemann-Pick disease, Sphingomyelinase deficiency</td>
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<tr>
<td>M-II. Benign proliferative macrophage diseases</td>
<td>Xanthoma disseminata, multicentric reticulo-histiocytosis</td>
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<tr>
<td>M-III. Hemophagocytic macrophage diseases</td>
<td>Fulminant hemophagocytic syndrome</td>
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<tr>
<td>M-IV &amp; V Monocytic leukemias</td>
<td>Acute monocytic leukemia, chronic myelomonocytic leukemia</td>
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<tr>
<td>M-VI. Malignant 5q35 histiocytosis</td>
<td>A variant of malignant histiocytosis with infiltration of soft tissues and bone with 5q35 translocation</td>
</tr>
<tr>
<td>M-VII. True macrophage lymphoma</td>
<td>The existence of a true disease entity is controversial</td>
</tr>
<tr>
<td>Langerhans’ cell</td>
<td></td>
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<tr>
<td>L-I. Clinically benign monoclonal Langerhans’ cell histiocytosis</td>
<td>Eosinophilic granuloma of bone, relapsing Langerhans’ cell histiocytosis, self-healing histiocytosis</td>
</tr>
<tr>
<td>L-II. Malignant monoclonal Langerhans’ cell histiocytosis</td>
<td>Progressive Langerhans’ cell histiocytosis [Letter-Siwe disease]</td>
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<tr>
<td>L-III. Langerhans cell lymphoma</td>
<td>Lymphoma</td>
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<td>L-IV. Dendritic cell lymphoma</td>
<td>Lymphoma</td>
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BE Favara