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Canine histiocytic neoplasia: cell lineages and disease classification (18-Sep-2002)

P. F. Moore

School of Veterinary Medicine, University of California, Davis, CA, USA.

Histiocytes differentiate from CD34+ committed stem cell precursors into macrophages and several dendritic cell (DC) lineages, which include epithelial DC or Langerhans cells (LC), interstitial DC in many organs (e.g. dermal DC), and interdigitating DC of T cell domains in peripheral lymphoid organs. Despite the large variation of clinical and pathological features of canine histiocytic diseases, most represent proliferations of cells of dendritic lineage.

Histiocytoma is a common, benign, cutaneous neoplasm of the dog. The tumor originates from epidermal LC. Histiocytomas usually occur as solitary lesions, which undergo spontaneous regression associated with CD8+ T lymphocyte infiltration. Multiple histiocytomas are infrequent and can be associated with delayed regression. Metastatic histiocytoma is readily confused with histiocytic sarcoma, but in some dogs spontaneous regression occurs in effaced lymph nodes. In other dogs the lesions either fail to regress, or spread beyond lymph nodes. Langerhans cell histiocytosis (LCH) is an extremely rare disease of dogs, which present with widespread cutaneous lesions that are almost confluent in affected regions. Histologically, the lesions are identical to histiocytomas. Immunohistochemical investigation has clearly shown that histiocytomas have the phenotype of epidermal Langerhans cells. They express CD1a, CD1b, CD1c, MHC class II, CD11c, and E-cadherin. Histiocytomas lack expression of CD4 and Thy-1, which are consistently expressed by histiocytes in cutaneous and systemic histiocytosis; the latter are reactive diseases of interstitial DC. Hence, cutaneous histiocytoma is a localized epidermal Langerhans cell tumor, and the rare examples of systemic spread of histiocytoma are best characterized as LCH similar to that observed in humans.

The histiocytic sarcoma (HS) complex encompasses a number of distinctive clinical entities. Histiocytic neoplasia that originates at a single site is called histiocytic sarcoma. This form of histiocytic sarcoma, which is often encountered on the extremities, has the best prognosis if treated early by surgical excision or by amputation of a limb. When spread to distant sites beyond the local lymph node occurs, the disease is then termed disseminated histiocytic sarcoma; this is more likely to occur unnoticed when primary lesions occur in cryptic sites (e.g. spleen, lung, and bone marrow). This latter form of HS is most like malignant histiocytosis (MH). MH is an aggressive, histiocytic neoplasm that arises in multiple sites simultaneously. Most lesions previously defined as MH are probably more correctly termed disseminated HS. The occurrence of true MH is difficult to establish because the lesions often occur in cryptic sites, and the existence of histiocytic neoplasia is only recognized after clinical signs have appeared and disease progression is advanced. HS and MH are capable of widespread metastasis, hence in time the 2 syndromes merge clinically and it is not always possible to differentiate true multicentric origin (MH) from widespread metastasis of disseminated HS.

The HS complex of diseases is best recognized in the Bernese Mountain Dog in which a familial association is apparent. Other breeds are predisposed to HS complex diseases and include Rottweilers, Golden Retrievers, and Flat-coated Retrievers. HS complex is not limited to just these breeds and can occur sporadically in any breed. Primary lesions of HS occur in spleen, lymph node, lung, bone marrow, skin and subcutis especially of extremities. Secondary sites are widespread, but consistently include liver and lung (with splenic primary), and hilar lymph node (with lung primary). Clinical signs include anorexia, weight loss, and lethargy. Other signs depend on the organs involved and are a consequence of destructive mass formation. Accordingly, pulmonary symptoms such as cough and dyspnea have been seen. CNS involvement (primary or secondary) can lead to seizures, incoordination and paralysis. Regenerative and non-regenerative anemia have been consistently documented in hemophagocytic HS. Lameness is often observed in periarticular HS.

The histological appearance of HS lesions is consistent regardless of location. Lesions are composed of sheets of large, pleomorphic, mononuclear cells and multi-nucleated giant cells that show marked cytological atypia and numerous bizarre

mitotic figures. Phagocytosis of red cells, leukocytes and tumor cells occurs, but is not prevalent in most forms of HS. However, in hemophagocytic HS this behavior is amplified. Neoplastic histiocytes manifest marked erythrophagocytosis and the infiltrates obliterate the splenic red pulp and invade red pulp sinuses.

MH and HS lesions express leukocyte surface molecules characteristic of DC (CD1, CD11c and MHC II). Diffuse expression of E-cadherin, Thy-1 and CD4 has not been observed in HS or MH in skin or other sites; this together with cytomorphology assists in the distinction of MH and HS from histiocytoma and reactive histiocytosis (such as cutaneous and systemic histiocytosis). In histiocytoma, the phenotype is quite similar to that of HS except for the expression of E-cadherin, which occurs especially in the cellular infiltrate immediately adjacent to the epidermis. In reactive histiocytosis, infiltration and proliferation of activated interstitial (dermal) DC, which consistently express CD4 and Thy-1, occurs. In hemophagocytic HS, histiocytes express CD11d instead of CD11c, and MHC II. Expression of CD1 molecules is uniformly low or occasionally moderate but with a patchy distribution. This phenotype is consistent with macrophage differentiation rather than DC differentiation in which abundant expression of CD1 and CD11c is expected.

The exact sublineage of DC involved in HS has not been determined in most instances. The most likely candidates include interdigitating DC in lymphoid tissues and perivascular interstitial DC in other involved tissues. Immunophenotyping and careful morphological assessment should also avoid confusion of HS and MH with large cell form of cutaneous T cell lymphoma, and poorly differentiated mast cell tumor.

Biographical Profile

Dr. Peter Moore received his PhD from the University of California, Davis in 1978 in Comparative Pathology. He has been a professor in the Department of Pathology, Microbiology and Immunology at the University of California, Davis since 1994, where his research has included histiocytosis in Bernese Mountain Dogs, lymphoma and inflammatory bowel disease in cats and gene therapy for canine x-linked SCID.

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