Histiocytic tumors represent a spectrum of neoplastic and immune-mediated diseases in dogs and cats. The treatments and prognoses for each of these diseases vary considerably. Until recently, much confusion surrounded the diagnosis and classification of histiocytic tumors, making it challenging to formulate consistent treatment recommendations for each tumor type. During the past decade, advanced molecular diagnostic techniques, particularly immunohistochemistry, have provided valuable insights into the cellular origins of these tumors. This in turn has facilitated more accurate tumor classification and helped to better define the biologic behavior of each tumor type.

What is a histiocyte?
The term histiocyte encompasses several cell lineages that perform an array of physiologic roles. All histiocytes are derived from hematopoietic precursor cells in the bone marrow, and are loosely classified into two categories:

1. Professional phagocytes – These encompass cells of the monocyte/macrophage lineage, including the sinusoidal macrophages of the spleen, alveolar macrophages of the lung, and Kupffer cells of the liver. These cells possess remarkable phagocytic capabilities but weak antigen-presenting capabilities.
2. Professional antigen-presenting cells – These include epithelial Langerhans’ cells, as well as dendritic cells which are present in both lymphoid organs (interdigitating and follicular dendritic cells) and non-lymphoid organs (interstitial dendritic cells). These cells possess weak phagocytic capabilities but serve a vital role in the presentation of processed antigens to naïve T-cells to initiate the adaptive immune response.

The various histiocytic cell populations may be distinguished from one another on the basis of immunohistochemical staining (see Table 1). The most important of these immunohistochemical markers from a diagnostic standpoint is arguably CD18, a marker expressed by all leukocytes, but which is present at much greater concentrations on the surface of histiocytes. Immunolabeling with CD18 and a panel of other markers will facilitate the differentiation of histiocytic tumors from other round cell tumors or anaplastic carcinomas/sarcomas (see Table 2). A histiocytic tumor should be considered any time an undifferentiated round cell tumor or sarcoma of uncertain cellular origin is diagnosed, particularly for tumors of the skin and subcutis, joints, spleen, or lymph nodes.

Immunohistochemistry has enabled the classification of several histiocytic diseases of clinical importance in dogs. Among these are: canine cutaneous histiocytoma (CCH), cutaneous and systemic histiocytosis (CH and SH), and histiocytic sarcoma (HS).

Canine cutaneous histiocytoma
Canine cutaneous histiocytoma (CCH) is a common benign neoplasm of the skin that usually presents as a solitary lesion in young dogs. Immunohistochemistry has revealed that cutaneous histiocytoma derives from epidermal Langerhans cells. Affected dogs are generally less than three years of age; however cutaneous histiocytomas may be seen in older dogs. Although surgical excision is usually curative, the majority of these tumors spontaneously regress within 1 to 2 months following diagnosis. Histologically, regressing lesions are often infiltrated by lymphocytes, suggesting that an immune mechanism mediates tumor regression.

A widely disseminated form of cutaneous histiocytoma called Langerhans’ cell histiocytosis (LCH), may present with numerous, confluent, ulcerated, rapidly progressive cutaneous lesions, and occasionally with lymph node metastasis. Like CCH, LCH may regress spontaneously, but often after a protracted clinical course. Dogs with LCH are often euthanized due to poor quality of life and failure of the lesions to regress in a timely fashion.

Reactive histiocytoses
The reactive histiocytoses comprise two related diseases, cutaneous histiocytosis (CH) and systemic histiocytosis (SH). The reactive histiocytoses are not true neoplastic diseases, but rather seem to result from dysregulation of the immune system. Ineffective antigen presentation to T-lymphocytes is thought to be the inciting stimulus for histiocytic proliferation in both diseases. The cell of origin for both CH and SH is an activated dermal (interstitial) dendritic cell. Both diseases are uncommon to rare.

CH usually presents with several rapidly growing dermal nodules or plaques that have a predilection for the face, pinna, nasal plane, and scrotum. Affected dogs are usually asymptomatic aside from the cutaneous lesions. Spontaneous regression may occur, but some form of immunosuppressive therapy is often needed to effect a lasting remission. Many lesions will respond to immunosuppressive doses of corticosteroids. In some cases, adjuvant immunosuppressants such as azathioprine, cyclosporine, or tetracycline/niacinamide may be required. The prognosis for dogs with CH is generally good, although some dogs may require long-term immunosuppressive therapy.

SH also presents with dermal lesions that have a similar site predilection to that seen in CH. However, SH is distinguished by histiocytic infiltrates in visceral organs and the presence of constitutional signs of illness, such as weight loss, anorexia, lethargy, and
conjunctivitis, in affected dogs. This disease has a clear predilection for the Bernese mountain dog, and familial clustering of cases suggests a genetic predisposition in this breed. Potent immunosuppressive agents (cyclosporine, leflunomide) are usually necessary to control clinical signs; glucocorticoids are usually ineffective. The prognosis for dogs with SH is guarded – although the lesions themselves are rarely life-threatening, the disease has an intractable clinical course and many affected dogs are euthanized due to poor quality of life.

**Histiocytic sarcoma**

Histiocytic sarcoma (HS) is an aggressive, devastating malignancy that may present as one of three anatomic forms. Localized HS occurs initially as a solitary lesion and can originate in virtually any organ, although the spleen, lymph nodes, joints, lung, and skin/subcutis are common primary sites. Disseminated HS (formerly known as malignant histiocytosis) refers to the polyosystemic form of this cancer. Dogs with disseminated HS frequently have lesions in the lung, liver, spleen, lymph nodes, and bone marrow, although, as with localized HS, virtually any organ may be affected. Hemophagocytic HS is a rare form of HS that affects primarily the spleen and bone marrow. Localized and disseminated HS arise from dendritic cells whereas hemophagocytic HS arises from macrophages. Bernese mountain dogs, Rottweilers, Golden retrievers, Labrador retrievers, and flat-coated retrievers are overrepresented for HS. The disease has been shown to be heritable in the Bernese mountain dog.

Dogs with localized HS may be asymptomatic but for the presence of a detectable mass, although the tumors are often rapidly growing and infiltrative. Localized HS of joints frequently produces lameness. Dogs with disseminated or hemophagocytic HS are usually clinically ill at the time of diagnosis. Lethargy, fever, anorexia, respiratory signs, and lymphadenomegaly are common presenting complaints. Anemia, thrombocytopenia, leukocytosis, and hypoalbuminemia may be identified on hematologic and serum biochemical screening.

Cytologically, HS are composed of pleomorphic round cells which may display multinucleation and erythrophagocytosis. In some cases, distinguishing HS from other pleomorphic round cell tumors may be challenging, and histopathology is recommended for definitive diagnosis of HS. Immunohistochemical staining may be required to differentiate HS from other anaplastic tumors (Table 2).

All HS are highly aggressive tumors. Even dogs presented for localized HS should be thoroughly staged for the presence of other lesions, as the metastatic rate for this cancer is reported to be 70-91%. Recommended staging tests for dogs with HS include a CBC, serum biochemistry profile, urinalysis, three-view thoracic radiography, abdominal ultrasonography, regional lymph node cytology (even for palpably “normal” nodes), and bone marrow aspirate cytology.

Treatment for HS depends upon the stage of the disease. Localized HS can be managed with aggressive surgery and/or radiation therapy. Amputation may be required for unresectable tumors on the limbs, although complete responses to primary radiation therapy can occur. Owing to the highly metastatic behavior of this tumor, adjuvant chemotherapy is recommended for all dogs with localized HS following local therapy. Dogs with disseminated HS are not surgical candidates owing to the widespread nature of their disease, and primary chemotherapeutic treatment is recommended for these dogs. The chemotherapy agent with the best documented efficacy against HS is the alkylating agent CCNU (lomustine). Approximately 25-50% of HS respond to CCNU. Doxorubicin chemotherapy may also be effective. Recent research suggests that bisphosphonate drugs such as clodronate or pamidronate may have primary antineoplastic effects against HS or may synergize with cytotoxic chemotherapy.

The prognosis for dogs with localized HS is guarded to poor. Dogs with localized HS treated with combined surgery (+/- radiation) and chemotherapy have the best prognosis, with reported survival times ranging from 586-980 days. Dogs with disseminated HS or unresectable localized HS which are treated with chemotherapy alone survive an average of 3-4 months. Successful therapy has not been described for hemophagocytic HS, and most affected dogs die within weeks of diagnosis.

**Feline histiocytic tumors**

Histiocytic tumors are rare in cats. Sparse data collected from a handful of case reports suggest that feline histiocytic sarcoma behaves in a similarly aggressive fashion to its canine counterpart. Few uniform staging or treatment recommendations can be made based on these reports, although application of the principles discussed above for canine HS is likely to be appropriate.

Feline progressive histiocytosis is a rare disease which has been described in a series of 30 cats. This disease initially presents with cutaneous nodules or plaques which often coalesce as the disease progresses. It has an indolent, though intractable, progressive behavior. No successful therapy has been described, and most cats eventually die of the disease, albeit after a protracted clinical course. Eventual progression of the histiocytic infiltration to visceral organs occurs in the terminal stages of disease.
### Table 1-Immunohistochemical differentiation of histiocytes

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<tr>
<th></th>
<th>CD1</th>
<th>CD4</th>
<th>CD11b</th>
<th>CD11c</th>
<th>CD11d</th>
<th>CD18</th>
<th>CD45/CD45RA</th>
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MD = macrophage  
DC = dendritic cell  
ADC = activated dendritic cell  
LC = Langerhans cell

### Table 2-Immunohistochemical differentiation of cutaneous round cell tumors

<table>
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<tr>
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<th>CD3</th>
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References

Hafeman SD, Varland D, Dow SW. Bisphosphonates significantly increase the activity of doxorubicin or vincristine against malignant histiocytosis cells. Vet Comp Oncol 2011;10:44-56.