Canine Histiocytic Diseases

Alastair R. Coomer, BVSc, MS
University of Florida

Julius M. Liptak, BVSc, MVetClinStud, FACVSc, DACVS, DECVS
Ontario Veterinary College, University of Guelph

ABSTRACT: Canine histiocytic diseases are an emerging spectrum of diseases characterized by proliferations of histiocytic cells. Nonneoplastic histiocytic disease (reactive histiocytosis, comprising cutaneous and systemic histiocytosis) is uncommon. Neoplastic histiocytic diseases include cutaneous histiocytoma, which is a benign histiocytic tumor, and localized and disseminated histiocytic sarcoma (previously known as malignant histiocytosis), which are malignant diseases. The differentiation of histiocytic diseases can be challenging. This article outlines the characteristics of each disease entity and details the clinicopathologic, histologic, immunohistochemical, prognostic, and therapeutic differences among them.

Histiocytic diseases are a commonly diagnosed but poorly understood spectrum of diseases in dogs and other species. Several different documented canine histiocytic proliferative diseases may be variations of the same disease or derived from cells of the same lineage. Published case reports and small case series provide some pertinent information on treatment and prognosis, but few concise and thorough reviews outline the specifics of these diseases. Furthermore, much confusion surrounds the terminology, presentation, and true prognosis of specific histiocytic diseases.

CLASSIFICATION

Canine histiocytic diseases have been classified into three major categories: nonneoplastic, nonmalignant neoplastic, and malignant neoplastic. These three categories encompass four syndromes: (1) reactive (cutaneous or systemic) histiocytosis (nonmalignant, nonneoplastic disease); (2) cutaneous histiocytoma (nonmalignant, neoplastic disease); (3) localized histiocytic sarcoma (LHS; malignant, neoplastic disease); and (4) disseminated histiocytic sarcoma (DHS; malignant, neoplastic disease) (see the box on page 203). Reactive histiocytosis results from immune system dysregulation. Cutaneous histiocytoma is a common, benign tumor of the adnexa. DHS is rare.

Histiocytes are tissue cells whose functions (primarily phagocytosis and antigen presentation) are related to their interactions with lymphocytes in inflamed tissues. Histiocytes may be classified as macrophages or as dendritic antigen-presenting cells (DAPCs). Macrophages are involved in the inflammatory process, contain high levels of lysosomal enzymes, and are capable of varying degrees of phagocytosis. The term DAPC encompasses follicular dendritic cells, Langerhans cells, interstitial dendritic cells, veiled cells, and interdigitating dendritic cells. All of these cells have typical dendritic morphology and low levels of lysosomal enzymes. They are
mostly incapable of phagocytosis and play a key role in antigen presentation to lymphocytes.  

**SPECIMEN PREPARATION AND ANALYSIS**

Definitive diagnosis of histiocytic disease depends on identifying the standard clinicopathologic and morphologic characteristics of histiocytes. Tissue specimens submitted for immunohistochemistry and cytology can be snap frozen or fixed with formalin. The advantages of snap freezing are a wide array of available stains and the increased likelihood of a definitive diagnosis. However, the equipment required for snap freezing (e.g., liquid nitrogen, isopentane, optimal cutting temperature compound) and for storage and transport of snap-frozen tissue is not widely available to general practitioners. Formalin fixation offers the next best alternative. Special stains for lysozyme and α1-antitrypsin, when positive, identify cells as being histiocytic rather than lymphoid or epithelial in origin. Cytologic characteristics of malignancy are then used to differentiate malignant from benign disease.

Cellular phenotype, which can be determined by immunophenotyping, has become the mainstay for definitive diagnosis of histiocytic diseases (Table 1). Immunophenotyping involves the use of monoclonal antibodies to differentiate specific surface antigens on lymphocytes and other cells of the immune system. Lympocytes generally express either CD3 or CD79a and CD18 antigens. Histiocytes do not express CD3 or CD79a, but they have 10-fold more CD18 than do lymphocytes. Histiocytes, therefore, can be accurately identified as those cells that have characteristic morphology, lack lymphoid immunophenotypic markers, and have abundant CD18.

If the specimen is snap frozen, immunohistochemical markers for CD3, CD11d, CD18, CD45RA, and CD79a are used to definitively determine whether a lesion is of histiocytic origin. Histiocytes in snap-frozen samples should strongly express CD18 but lack expression of CD3, CD11d, CD45RA, and CD79a. This panel (CD18+, CD3−, CD11d−, CD45RA−, CD79a−) differentiates histiocytic disease from epitheliotrophic lymphoma (CD3+ and CD79a+), but it cannot differentiate between the different histiocytic diseases because all histiocytes are positive for CD18. If the specimen has been fixed in formalin, then CD18 is the only reliable marker that can be used to diagnose histiocytic disease.

Further differentiation of histiocytes into those of macrophage or DAPC origin requires identification of positive CD11b, CD14, and CD68 markers or CD1, CD11c, major histocompatibility complex class II (MHC II), and intercellular adhesion molecule 1 (ICAM-1) markers, respectively. DAPCs can also be distinguished as activated or nonactivated based on whether they stain positively or negatively for CD4 and subtypes of CD1, depending on the disease present. These markers can be identified only in snap-frozen specimens. It is unknown whether definitive diagnosis of the cell of origin influ-
Table 1. Immunohistochemical Markers and Tissue Preparation Techniques Used to Identify Cellular Origin

<table>
<thead>
<tr>
<th>Cellular Origin</th>
<th>Immunohistochemical Markers</th>
<th>Tissue Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>CD11a, CD44</td>
<td>Frozen</td>
</tr>
<tr>
<td></td>
<td>CD18, CD45</td>
<td>Fixed or frozen</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>CD3, CD79a (Mb-1)</td>
<td>Fixed or frozen</td>
</tr>
<tr>
<td>• B lymphocyte</td>
<td>CD21-like</td>
<td>Frozen</td>
</tr>
<tr>
<td>• Reactive lymphocyte</td>
<td>CD8 (α, β), TCRαβ</td>
<td>Frozen</td>
</tr>
<tr>
<td>• T lymphocyte</td>
<td>TCRγδ</td>
<td>Frozen</td>
</tr>
<tr>
<td>Macrophage</td>
<td>CD11b, CD18, CD14, CD68</td>
<td>Frozen</td>
</tr>
<tr>
<td>Myeloid DAPC</td>
<td>CD1 (a, b, c), CD11c, CD18, CD54 (ICAM-1), MHC II</td>
<td>Frozen</td>
</tr>
<tr>
<td>Myeloid DAPC (activated)</td>
<td>CD1 (a, b, c), CD4, CD11c, CD54 (ICAM-1), CD90 (Thy-1), MHC II</td>
<td>Frozen</td>
</tr>
</tbody>
</table>

aHistiocyte
ICAM = intercellular adhesion molecule, Mb = B-cell marker, MHC = major histocompatibility complex, TCR = T-cell receptor

ences the clinical management and prognosis for the various histiocytic diseases in dogs. Clinicians should contact individual commercial veterinary pathology laboratories regarding the availability and preparation of tissues for immunohistochemical stains (see the box below).

NONMALIGNANT, NONNEOPLASTIC DISEASE

Canine reactive histiocytosis, whether systemic histiocytosis (SH) or cutaneous histiocytosis (CH), is a result of immune system dysregulation and primarily affects the skin and subcutis. It is characterized by multiple nonpruritic, painless cutaneous plaques and nodules that are predominantly located on the head, neck, perineum, scrotum, and extremities. In dogs with SH, lesions are also evident in the nasal cavity (mucosae), palpebrae, sclera, lung, spleen, liver, and bone marrow. Multiple lymph node involvement is also common. SH is more commonly observed in Bernese mountain dogs, rottweilers, and golden and Labrador retrievers than in other breeds. Patient age at diagnosis of SH is usually 4 to 7 years; male dogs are more frequently reported affected than are females. No breed or sex predilections are seen in dogs with CH; in these dogs, age at diagnosis ranges from 3 to 9 years.

The major clinical differentiation between CH and SH is the number of concurrent lesions and the simultaneous multiorgan involvement in dogs with SH. With SH, because multiple organ systems are involved, clinical signs correspond with lesion location and often include anorexia, marked weight loss, stertorous respiration, conjunctivitis, and chemosis. Physical examination reveals multiple cutaneous and subcutaneous nodules or plaques (up to 4 cm in diameter) on the scrotum, nasal planum, nasal apex, and eyelids. The lesions and clinical course of reactive histiocytosis are generally slowly progressive. In rare cases, the lesions may regress spontaneously, especially during the early stages of disease.

The skin lesions of CH and SH are histologically identical and are characterized by an angiocentric, pleo-

(text continues on page 208)
cellular infiltrate composed of lymphocytes, neutrophils, and activated interstitial, myeloid, perivascular DAPCs of the dermis.\textsuperscript{2,3,18} In SH, cutaneous lesions may also be characterized by a multinodular, coalescing-to-diffuse pleocellular infiltrate, predominantly in the deep dermis and subcutis. The infiltrate consists of large round-to-oval histiocytes with large monomorphic nuclei. This histologic appearance is consistent with a nonneoplastic reactive process.\textsuperscript{16} Lesions often form dense perivascular cellular cuffs; this is the major histologic difference between reactive histiocytosis lesions and cutaneous histiocytoma. Immunophenotyping of snap-frozen specimens reveals dense accumulations of activated DAPCs that stain positive for the immunohistochemical markers CD1, CD4, CD8, CD11b, and CD90 (Thy-1); this also supports a nonneoplastic reactive process (Table 2).\textsuperscript{2,16} However, these markers are not specific for neoplastic or nonneoplastic disease.

In dogs with CH or SH, surgical excision is successful for local disease but does not prevent the development of new lesions.\textsuperscript{18} Immunosuppressive and immunomodulatory drugs have been used with mixed results. Because SH and CH are caused by immune system dysregulation, they may respond favorably to immunosuppressive therapy; however, this therapy must be prolonged (i.e., lasting many months).\textsuperscript{18} Response to corticosteroids varies but may be as high as 50% in dogs with CH.\textsuperscript{18,24} Cyclosporine A and leflunomide are generally more successful in treating reactive histiocytosis and are necessary in cases refractory to corticosteroids.\textsuperscript{18} Ocular lesions may be difficult to resolve and may require ophthalmic preparations of cyclosporine A (1 drop q12h of 0.2% to 1.0% drops).\textsuperscript{16}

Dogs with CH or SH have a guarded prognosis because the clinical course of reactive histiocytosis is usually prolonged; therefore, patients require prolonged immunosuppressive therapy. While dogs rarely die of their disease, the need for chronic medication and the frequent recurrence of disease result in most affected dogs being euthanized.\textsuperscript{18,21–23} In one report, therapeutic success and induction of remission were reported in only 6 of 26 dogs with SH treated with cyclosporine A, leflunomide, or doxorubicin.\textsuperscript{18} These dogs required long-term or intermittent therapy to prevent recurrence. In this report, systemic corticosteroid therapy failed to induce regression of lesions in most dogs.

**NONMALIGNANT, NEOPLASTIC DISEASE**

Cutaneous histiocytoma is a benign epitheliotropic neoplasm originating from intraepidermal DAPCs (Langerhans cells).\textsuperscript{2} Canine cutaneous histiocytoma occurs most frequently in dogs younger than 3 years, although it is occasionally diagnosed in older dogs.\textsuperscript{20} A breed predisposition for multiple cutaneous histiocytomas has been reported in shar-peis.\textsuperscript{16,20}

C utaneous histiocytomas appear as small, firm, dome- or button-shaped dermoepithelial masses of the head, pinnae, neck, or limbs (Figure 1).\textsuperscript{2} They are fast growing, nonpruritic, painless, usually solitary, and often less than 2.5 cm in diameter.\textsuperscript{16,20} Solitary lesions may spontaneously regress within 6 weeks; multiple histiocytomas may persist longer because of overlap between the regression of old masses and development of new masses.\textsuperscript{16} Persistent nodules may ulcerate and pose a risk for bacterial infection. Regional lymphadenomegaly (due to migrating histiocytoma cells) has been reported with cutaneous histiocytoma and usually resolves with the skin lesions;\textsuperscript{16} however, if regional lymphadenopathy is present, malignant histiocytic disease should be suspected.\textsuperscript{16} Nodal biopsy with immunohisto-
chemistry is required to rule out malignant histiocytic disease.

Cytologic characteristics of samples aspirated from histiocytomas include clumps of round or oval cells with a variable amount of pale basophilic cytoplasm (lacking vacuolation) and round-to-ovoid, eccentrically placed nuclei with finely granular chromatin and inconspicuous nucleoli.

Histologically, cutaneous histiocytomas appear as poorly demarcated, nonencapsulated, intracutaneous nodules and are therefore difficult to differentiate from nonepitheliotrophic or epitheliotrophic cutaneous lymphoma (mycosis fungoides).20 Unlike the perivascular aggregation of reactive histiocytosis, cutaneous histiocytomas are organized into uniform sheets of histiocytes that penetrate the dermis or subcutis. The diffuse population of monomorphic round cells with large, round-to-oval, indented or twisted vesicular nuclei may be densely packed in the deeper layers of the dermis.16 Collagen fibers and skin adnexae may be displaced. Because of the epidermal invasion and intraepidermal aggregation of lymphocytes, immunohistochemical phenotyping may be required to rule out epitheliotrophic lymphoma.16,20 Cutaneous histiocytomas stain positive for CD1 but, unlike reactive histiocytosis samples, usually stain negative for CD4 and CD90 (Thy-1).18 This phenotype is consistent with that of nonactivated epidermal DCs18 and is a major difference between cutaneous histiocytoma and reactive histiocytosis. However, the absence of CD4 staining is not definitive for cutaneous histiocytoma.

While surgical excision or cryosurgery is generally curative, histiocytomas may spontaneously regress within 6 weeks (for solitary lesions) to 10 months (for multiple lesions).16,20 Surgical excision is recommended for any solitary mass that has not spontaneously regressed within 3 months.16,20 Because immunosuppressive drugs may interfere with spontaneous regression by inhibiting T-cell infiltration, their use is contraindicated; hence, every effort should be made to differentiate cutaneous histiocytoma from nonneoplastic reactive histiocytosis.16

After surgical excision or spontaneous regression of single or multiple lesions, the prognosis for dogs with histologically confirmed cutaneous histiocytoma is excellent. The marked difference between the prognosis for this neoplastic disease and that for nonneoplastic reactive histiocytosis is due to the fact that therapy for cutaneous histiocytoma is curative and limited to one procedure rather than prolonged and immunosuppressive.

**MALIGNANT DISEASE**

**Localized Histiocytic Sarcoma**

LHS is a rapidly growing, solitary, locally invasive soft tissue mass with moderate-to-high metastatic potential.2,6,18 LHS has been reported in many breeds, with flat-coated retrievers, Bernese mountain dogs, Labrador retrievers, and rottweilers being overrepresented.2,11,18 Most affected dogs are 6 to 11 years of age.

Lesions may arise from a single site. Predilection sites include the subcutis and underlying tissues of the extremities. Primary lesions may also be found in the periarticular soft tissues, spleen, lung, brain, nasal cavity, and bone marrow.2,3,7,9,18,25–27 Periarticular lesions often encircle the joints and involve the joint capsule, tendons, and skeletal muscles.16 LHS is locally invasive, frequently invading the deep dermis and the underlying skeletal muscle and fascia. Metastatic lesions, if present, are seen in draining lymph nodes, with a 60% metastatic rate reported in one study.23 If organ systems other than the skin (e.g., the spleen) are involved, a more aggressive, hemophagocytic form of the disease is likely and the metastatic rate is increased, as is the clinical suspicion of DHS.20

Clinical signs are generally related to local disease and the organ of involvement. Most dogs with LHS present with palpable cutaneous or subcutaneous masses and are not systemically ill, unlike dogs with DHS.9 Thorough clinical staging includes palpation and aspiration of regional lymph nodes, bone marrow aspiration, abdominal ultrasonography, and three-view thoracic radiogra-
phy to assess for multiorgan involvement and metastasis and to differentiate LHS from DHS.25,27

The typical histologic findings for LHS include an invasive, highly cellular mass of pleomorphic histiocytic cells. These cells are characterized by anisocytosis with abundant eosinophilic and finely granular to foamy cytoplasm. The nuclei vary markedly in form and size and are often located centrally with prominent nucleoli of varying sizes. Multinucleated cells and mitotic figures, including those with abnormal forms, are frequently observed.3,4,7,16

 Immunohistochemical evaluation often yields low-to-moderate numbers of lysozyme-positive cells and large numbers of vimentin-positive cells.3,7 All cells should be negative for both T- (e.g., CD3) and B-lymphocyte (e.g., CD79) markers.3,7,28 Nonactivated DAPCs stain positively for the immunohistochemical markers CD1b, CD1c, and, rarely, CD90 (Thy-1).2,10,18 Some histiocytic sarcomas also stain positively for CD11d; however, it is not known whether this finding is unique to histiocytic sarcomas.16 The critical difference between the immunophenotype of malignant LHS and that of benign cutaneous histiocytoma is expression of CD4, a marker for activation of myeloid DAPCs. Many more cells will be CD4 positive in cases of LHS compared with cases of cutaneous histiocytoma.2,18

Aggressive surgical resection of cutaneous LHS is recommended (Figure 2).2 Surgical margins should be the same as those used for soft tissue sarcomas: 3-cm lateral margins and a deep margin of at least one fascial layer.29 Limb amputation is recommended for nonmetastatic periarticular LHS.30 Radiation therapy has not been investigated in the treatment of gross or microscopic incompletely resected LHS, but other round cell tumors (e.g., lymphoma, mast cell tumors) are sensitive to irradiation.7 Hence, full-course fractionated radiation therapy protocols should be considered for incompletely resected or unresectable LHS. Because the potential for distant metastasis is moderate to high, postoperative chemotherapy should also be considered.18 However, the efficacy of different postoperative chemotherapy drugs and protocols in the treatment of dogs with LHS has not been evaluated. Based on the current treatment recommendations for DHS, single-agent protocols using either doxorubicin or lomustine are suggested.24

The prognosis for dogs with LHS of the skin and subcutis is unknown, but in one small, retrospective series, neither local tumor recurrence nor metastasis was observed following resection with wide surgical margins and no adjunctive treatment in all five dogs with long-term follow-up.2 However, distant metastasis is reported in 38% to 60% of dogs.25 Time to metastasis has not been reported. In contrast, the prognosis for dogs with LHS of the internal organs (Figure 3), such as the spleen, is poor, with a median survival time (MST) of 1 month and a 0% to 20% 1-year survival time.2,19,31 Poor prognostic factors in dogs with splenic histiocytic sarcomas include lymphoid: fibrohistiocytic ratio, mitotic index, and histologic grade.31,32 Dogs with a lymphoid: fibrohistiocytic ratio of greater than 40% have a 1-year survival probability of 87%; if the ratio is less than 40%, the 1-year survival probability is 55%.31 Dogs with grade III fibrohistiocytic nodules have a 1-year survival rate of 32%, which is significantly worse than the rates of 57% and 61% for dogs with grade I and II lesions, respectively.31 The MST for all
dogs with LHS has not been reported in the literature. One dog with an LHS of the tendon sheath of the biceps brachii muscle had a survival time of only 4 months.1

The prognosis for dogs with synovial LHS is very poor.30 In a series of 18 dogs with synovial LHS, the overall MST was 5.3 months, the MST for dogs undergoing amputation (with or without chemotherapy) was 6 months, and the metastatic rate was 91%.30 The use of postoperative chemotherapy may improve the prognosis for dogs with LHS.

LHS in dogs may be analogous to malignant fibrous histiocytoma in humans. The term malignant fibrous histiocytoma has historically been used to describe a collection of unspecified soft tissue sarcomas of different cell origins that are characterized by multinucleated giant cells and commonly diagnosed in the extremities.2,33 This umbrella encompasses fibrosarcomas, leiomyosarcomas, rhabdomyosarcomas, liposarcomas, synovial cell sarcomas, and histiocytic sarcomas. However, this description is somewhat inaccurate in dogs; therefore, the term LHS is preferred by most veterinary pathologists.2,33

**Disseminated Histiocytic Sarcoma**

DHS is the preferred term for the disease historically known as malignant histiocytosis.2 DHS is a systemic proliferation of tissue macrophages (histiocytes) or myeloid DAPCs and their precursors.2,6,15,17 Many reports, however, describe the cellular origin as unknown.2,3 In such cases, it is difficult to definitively diagnose DHS.

DHS is an aggressive, multisystem disease characterized by multiple tumors in several organs, with the spleen, lung, and bone marrow involved primarily and the liver and lymph nodes secondarily.2,3,7,17,18,28 Multiple solid, pale tumors in these organs and others are characteristic at postmortem examination.3,7,17,18,28 Retrievers, rottweilers, and Bernese mountain dogs are overrepresented.2,10,18 No sex predisposition has been reported, and dogs of any age can be affected.2,18 In Bernese mountain dogs, DHS is a genetic disease with a polygenic mode of inheritance.3

Dogs with DHS often have nonspecific clinical signs and physical examination findings that indicate multisystem involvement. Cutaneous and subcutaneous lesions are common and must be differentiated from those of LHS based on clinical staging, as described...
above. DHS and SH are differentiated based on immunohistochemistry and clinical staging. Clinical signs specific to organ system involvement include dyspnea (pulmonary masses with neoplastic involvement of the hilar lymph nodes), lameness (extensive proliferative bone marrow lesions with associated destruction of the surrounding bone), and various neurologic signs (associated with brain and spinal cord lesions). Lymphadenomegaly, hepatomegaly, and splenomegaly are also often present. Neurologic signs, such as paraplegia or paralysis, are reported in 38% of dogs. In addition to clinical staging, diagnosis of DHS is based on abdominal ultrasonography, three-view thoracic radiography, bone marrow aspiration and cytology, and clinical, histopathologic, immunohistochemical, and immunophenotypic findings.

Radiographs may show pulmonary consolidation, nodular opacities, pleural effusion, diffuse interstitial infiltrations, and hepatosplenomegaly. On ultrasonography, hypoechoic nodules are commonly seen in the spleen; some may distort the splenic margin. The liver is the second most commonly affected organ. Hepatic lesions can be hypoechoic, hyperechoic, or of mixed echogenicity. Other common ultrasonographic findings include hypoechoic nodules in the kidneys and mesenteric or medial iliac lymphadenomegaly. Results of a recent study suggest that the ultrasonographic appearance of canine abdominal DHS is nonspecific and that nonhistiocytic disease (e.g., hemangioma, soft tissue sarcoma) can be ruled out only by cytologic or histopathologic evaluation in these patients.

Hematologic findings include cytopenia (e.g., autoimmune hemolytic anemia, leukopenia, thrombocytopenia) associated with cellular phagocytosis by neoplastic macrophages. Serum biochemical abnormalities are variable, but hyperbilirubinemia has been reported frequently. Dogs with thrombocytopenia may also have a prolonged coagulation profile indicative of (imminent) disseminated intravascular coagulation. Ferritin has shown promise as a biochemical marker in dogs with concurrent hyperferritinemia, especially when the owner elects chemotherapy. Serum ferritin levels may be reduced with successful chemotherapy.

Cytology from direct or image-guided aspiration of accessible masses yields moderate numbers of intermediate-to-large histiocytic cells, either as single cells or in small aggregates. The cells may be round, fusiform, or irregularly shaped. They contain abundant granular, pale basophilic cytoplasm (Figure 4) and oval to reniform eccentric nuclei with prominent, sometimes multiple, nucleoli. Cytoplasmic hemosiderin granules and vacuolation are common. Cytophagia has been reported and assists in the diagnosis of DHS. Cytology from bone marrow aspirates shows infiltrates of neoplastic cells in association with erythroid and myeloid hyperplasia.

Histologic examination of grossly abnormal organs reveals infiltration of the organ with sheets of a pleomorphic population of atypical histiocytic cells that have finely granular or vacuolated eosinophilic cytoplasm and pleomorphic, anisokaryotic nuclei with pale to granular chromatin and prominent nucleoli. Hemosiderin and erythrocytes are occasionally seen in tumor cells, especially in splenic masses. Multinucleate giant cells may be present (Figure 5), and mitotic figures are occasionally noted. Poor encapsulation of cellular infiltrates with necrotic cores that obliterate surrounding normal tissue architecture has been infrequently reported.

DAPCs of DHS should stain positive for CD1b, CD1c, and, rarely, CD90 (Thy-1). LHS also positively expresses these immunohistochemical markers; therefore, LHS and DHS can only be differentiated based on clinical presentation, physical examination findings, and results of clinical staging. It has been proposed that the origin of malignant cells be confirmed by immunohistochemistry. In one human study, the use of additional staining techniques showed that samples from many patients originally diagnosed with DHS lacked histo-
Cytomembrane markers. These patients were subsequently found not to have DHS. We have used immunohistochemistry to diagnose DHS postmortem in a subset of dogs in which multicentric lymphosarcoma was originally diagnosed but did not respond to conventional therapy.

An effective treatment for dogs with DHS has not been described. Surgical resection of cutaneous lesions or affected organs (e.g., spleen, liver lobe, lung lobe) is generally not recommended unless it will provide some palliative benefit. Chemotherapy is the recommended treatment, but there are few reports of successful remission, with most dogs having rapid clinical progression and deterioration because of the very aggressive behavior of DHS. Lomustine (60 to 90 mg/m² q3–4wk) was used with some success as a single agent in an unpublished multiinstitutional study. In this study, the response rate in 56 dogs with gross measurable disease treated with lomustine alone was 46%. The median remission duration in the 26 dogs that responded to therapy was 85 days, and the MST was 172 days in these dogs. If lomustine-based chemotherapeutic protocols for treatment of DHS are unsuccessful, protocols involving cyclophosphamide, vincristine, prednisone, mitoxantrone, dacarbazine, and/or etoposide have been described. A small group of dogs with DHS reportedly responded to an immunotherapy protocol involving treatment with a human cytotoxic T-cell line.

The human equivalent of DHS is disseminated Langerhans cell histiocytosis, which is an accumulation of tissue histiocytes in one or multiple organs or tissues that generally manifests with extensive multiorgan disease and fail-

Figure 5. Lymph node aspirate (Wright’s-Giemsa) from the same dog as in Figure 4. The cell at the center of the field exhibits cytomegaly and extreme multinucleation.
Treatment is palliative and includes a wide spectrum of drugs (e.g., corticosteroids, chemotherapeutic agents [including vinca alkaloids and antimetabolites]) and immunomodulation (including immune-system up-regulation). A trial of the antimetabolite 2-chlorodeoxyadenosine in human patients with refractory, relapsed or widespread disease achieved relative success. The prognosis for dogs with DHS is poor. Based on the few available survival data, the MST is 106 days (range: 2 to 884 days) and the 1-year survival rate is 0% to 30%. Thrombocytopenia, hypoalbuminemia, and histologic evidence of giant cells are all poor prognostic factors. In some reports, dogs presented with a clinical sign that caused death, and DHS was diagnosed at necropsy; in others, the dog was euthanized at the time of diagnosis or soon after because of rapid clinical deterioration. Few reports of treatment, response, and survival rates in dogs with DHS are available.

CONCLUSION

Diagnosis, staging, treatment, and prognostication of histiocytic diseases pose a challenge for the clinician. While the initial clinical presentation of the various histiocytic diseases is similar, the management and prognosis vary considerably. Accurate diagnosis and clinical staging are important to determine treatment options and prognosis. There is a distinct difference between dogs with LHS and DHS, and a histologic diagnosis of histiocytic sarcoma should not be interpreted as a poor prognosis until the appropriate staging tests have been conducted to differentiate LHS from DHS.

ACKNOWLEDGMENTS

The authors thank Dr. Rebekah Gunn for her assistance with the cytologic images.

REFERENCES

1. Which of the following statements about histiocytes is false?

a. Histiocytes are tissue macrophages whose functions are related to their interactions with lymphocytes in inflamed tissues and consist primarily of phagocytosis and antigen presentation.

b. Macrophages are involved in the inflammatory process, have high lysosomal enzyme content, and are capable of varying degrees of phagocytosis.

c. DAPCs have typical dendritic morphology and low levels of lysosomal enzymes, are mostly incapable of phagocytosis, and play a key role in antigen presentation to lymphocytes.

d. Histiocytic phenotype cannot be differentiated using immunohistochemistry and is not clinically important.

2. Which of the following results of immunohistochemistry conducted on a formalin-fixed specimen suggests histiocytic disease?

a. CD3+, CD18-, CD45+, CD79-

b. CD3-, CD18+, CD45-, CD79-

c. CD3+, CD18+, CD45+, CD79+

d. CD3-, CD18-, CD45-, CD79-

3. Lesions typical of reactive histiocytosis are

a. nonpruritic and painless, grow slowly, and rarely regress.

b. nonpruritic and painless, grow rapidly, and rapidly regress.

c. pruritic and painful, grow slowly, and rarely regress.

d. pruritic and painful, grow rapidly, and rapidly regress.
4. Long-term medical immunosuppression is preferred over local surgical excision for the management of reactive histiocytosis because
a. middle-aged dogs are never good surgical candidates.
b. multiple lymph node involvement is common in cases of SH.
c. distant de novo masses are common with CH.
d. b and c

5. A solitary, small, firm, dome-shaped, dermoeppithelial mass on the neck of an otherwise healthy 1-year-old shar-pei should raise suspicion for
a. SH.  c. LHS.
b. cutaneous histiocyteoma.  d. DHS.

6. If the mass described in question 5 were snap frozen and submitted for immunohistochemical staining, results of CD1+, CD11c+, CD18+, MHC II+, ICAM-1+, CD4-, and CD90 (Thy 1)- would be consistent with a
a. reactive process such as SH.
b. benign neoplastic process such as cutaneous histiocy-toma.
c. malignant neoplastic process such as LHS.
d. malignant neoplastic process such as DHS.

7. Metastasis (local lymph node involvement) has been reported in ___ of cases with LHS.
   a. less than 1%  c. 60%
   b. 5% to 15%  d. more than 90%

8. ______ is a poor prognostic factor associated with splenic LHS.
   a. Lymphoid:fibrohistiocytic cell ratio <40%
   b. High mitotic index
   c. High histologic grade
   d. all of the above

9. DHS and LHS can be distinguished based on
   a. signalment.
   b. location of lesions and/or metastasis.
   c. immunohistochemistry.
   d. clinical presentation, physical examination, and clinical staging.

10. Which of the following statements about DHS is true?
    a. The prognosis for dogs with DHS is poor, with an MST of 106 days and a 0% to 30% 1-year survival rate.
    b. Thrombocytopenia, hypoproteinemia, and histologic evidence of giant cells are all poor prognostic factors.
    c. Lomustine has been used with excellent results, achieving median remission rates of more than 85% and longer than 900 days.
    d. a and b