Owing to the rapid increase in immunohistochemical markers available for determining leukocyte subsets, a large number of different diseases of histiocytic origin have been described recently in dogs and cats. Unfortunately, many of the immunohistochemical markers described are not widely available and some are not amenable to use on formalin fixed paraffin embedded samples. Additionally, optimal therapy and clinical outcomes are not always well described for many of these conditions, adding to the confusion. A brief description of the identified syndromes follows, as well as what is known about treatment and outcome when appropriate.

**Histiocytoma**
Histiocytoma is a common, benign, cutaneous tumor of the dog. Histiocytomas usually occur as solitary lesions, and most will spontaneously regress. Although histiocytomas can be seen in dogs of any age, they are most common in younger dogs. They generally present as solitary raised, tan-pink, fleshy cutaneous masses. Most can be diagnosed through cytologic evaluation, although occasionally histopathology may be necessary. If the lesions are ulcerated, secondarily infected or pruritic, conservative marginal excision can be performed and is curative.

**Transmissible Venereal Tumor**
Transmissible venereal tumor (TVT) is a horizontally transmitted clonal round cell tumor typically involving the external genitalia, although oral and nasal cavity and other sites can occasionally be involved. The incidence is higher in warmer climates with a high frequency of free roaming, sexually intact dogs. TVT is transmitted across major histocompatibility complex (MHC) barriers, generally through sexual activity. TVTs from across the world have a relatively conserved, atypical karyotype (59 chromosomes), supporting the contention that the same cells have been passed from dog to dog. TVT is generally classified as a histiocytic neoplasm, owing to positive staining for lysozyme and ACM1, both macrophage-specific markers. Lesion typically present as well vascularized, friable, erythematous masses arising from the penis or vagina/vestibule. Multifocal disease and/or regional lymph node involvement is possible.
Some TVTs will undergo spontaneous regression, likely an immune-mediated rejection of this foreign tissue. The mainstay of therapy for clinical TVT is single-agent vincristine, which induces complete responses in 90-95% of patients. Weekly therapy is typically pursued, until 2 treatments beyond clinical remission. Both doxorubicin and radiation therapy have been reported to be efficacious in vincristine-refractory cases.

**Langerhans Cell Histiocytosis**
Langerhans cell histiocytosis is a rare disease characterized by extensive regional infiltration by histiocytes, which appear cytologically and histologically similar to those observed in simple histiocytomas; however, systemic dissemination occurs. The outcome appears to be very poor in dogs with this disease, and effective medical therapy has not been described. Localized lesions may be amenable to surgery or radiation therapy in the early stages. In humans, prednisone, vinblastine, cytosine arabinoside, 2-chlorodeoxyadenosine, etoposide and interferon-alpha appear to have some efficacy.

**Systemic Histiocytosis and Cutaneous Histiocytosis**
Systemic histiocytosis (SH) is most commonly recognized in Bernese Mountain Dogs, but has been observed in other breeds occasionally. SH is a generalized histiocytic proliferative disease with a marked tendency to involve skin, ocular and nasal mucosae, and peripheral lymph nodes. Clinical signs can include anorexia, marked weight loss, respiratory stridor and conjunctivitis. Multiple ulcerated
cutaneous nodules can be present throughout the skin and palpable peripheral lymphadenopathy is common.

Cutaneous histiocytosis is a histiocytic proliferative disorder that primarily involves skin and subcutis and rarely extends to the local draining lymph nodes. If disease extends beyond the nodes, a diagnosis of SH would be made. CH occurs in a number of breeds.

Both CH and SH cells possess markers consistent with an “activated” dendritic cell phenotype. This, combined with the waxing and waning course and response to immunosuppressive therapies, suggests a reactive rather than a true transformed neoplastic condition.

As mentioned, above, CH and SH lesions may spontaneously regress, so careful observation for 3-5 weeks may be appropriate. Immunosuppressive doses of corticosteroids may be used, but most patients require additional immunosuppressive therapy in the form of cyclosporine or leflunomide. Recent reports suggest that treatment with tetracycline and niacinimide may also be efficacious. Exposure to infectious agents and vaccines should be avoided in these patients.

**Histiocytic Sarcoma / Malignant Histiocytosis**

**Clinical presentation**

Histiocytic sarcoma (HS) and the related disorder, malignant histiocytosis (MH), occur with greatest frequency in Bernese Mountain Dogs (BMD), Rottweilers, Flat Coated Retrievers, Golden Retrievers and sporadically in many other breeds. Histiocytic sarcomas occur as solitary lesions in spleen, lung, subcutis and periarticular tissue. Histiocytic sarcomas can also occur as multiple lesions in single organs. MH is a multi-system, rapidly progressive disease in which there is simultaneous involvement of multiple organs such as spleen, lymph nodes, lung, subcutaneous tissues and/or bone marrow.

In the BMD breed up to 30% of individuals may be affected. The mean age of onset is 6.5 years, and 70% of affected individuals have a first- or second-degree relative with HS/MH, suggesting a strong hereditary component. Perdigree analysis suggests an oligogenic mode of inheritance. Recurrent losses of chromosomal regions incorporating the tumor suppressor genes CDKN2A/B and Rb1 have been identified in the majority of evaluated tumors.

Clinical signs of HS/MH include anorexia, weight loss, and lethargy. Other signs depend on the organs involved and are a consequence of destructive mass formation. Accordingly, pulmonary signs such as cough and dyspnea have been observed. Lameness is often observed in periarticular HS.

A distinctive syndrome called *hemophagocytic HS* has been described recently. This disease is frequently confused with immune-mediated hemolytic anemia/thrombocytopenia. Regenerative anemia and thrombocytopenia have been consistently documented, and affected dogs also frequently demonstrate hypoalbuminemia and hypocholesterolemia. Diffuse splenomegaly is a common finding, and bone marrow and hepatic infiltration can be observed. The outcome is generally poor for these cases, although splenectomy may be considered for solitary splenic lesions.

**Diagnosis and staging**

Needle aspiration cytology of lesions accessible either peripherally or via ultrasound guidance, combined with signalment and clinical presentation information, can often lead to a high suspicion of HS/MH. Histology +/- immunohistochemistry is often required for a definitive diagnosis however. A recent study suggested that measurement of serum ferritin may be a useful complement to microscopic evaluation for supporting a diagnosis of histiocytic neoplasia.

Once a suspicion of HS/MH has been established through cytology/histopathology, extensive staging is appropriate. In addition to standard presurgical blood work, this should include needle aspiration of any accessible regional lymph nodes (for peripheral lesions), whether clinically enlarged or not, abdominal ultrasound +/- needle aspiration cytology of any structural abnormalities, and 3-view thoracic radiographs. The information obtained from complete staging is vital, as the first line of treatment for disease that is confined to the local site (+/- regional lymph node) is surgical excision.

**Therapy and prognosis**
Some localized HS affecting skin and subcutis have been cured by early surgical excision, and radiation therapy can be considered in cases of incomplete excision. In the case of periarticular HS, amputation of the affected limb is indicated, and the outcome following this procedure is invariably superior to that obtained with any “limb sparing” local treatment options. Owing to the comparatively poor outcome with surgery alone (reported median survival times are approximately 5 months), adjuvant chemotherapy is offered for all cases of HS.

Disseminated HS (including MH) is not readily treated surgically. Unfortunately, responses to chemotherapy are generally incomplete and brief. The agent that has been utilized the most for medical therapy of HS/MH is lomustine (CCNU). 2 separate investigations report overall response rates of 29-46% in dogs with measurable disease (10-15% complete responses), with median response durations of 85-96 days. One study investigating the outcome following surgery and CCNU for localized HS reported a median survival time of 568 days. Other agents where there is at least preliminary evidence of efficacy include paclitaxel, liposomal doxorubicin and liposome clodronate. Anecdotally efficacy has been reported with single-agent doxorubicin and combination protocols as pursued for lymphoma, as well as with the tyrosine kinase inhibitor toceranib. Etoposide appears to have clinical activity in humans with HS/MH.

Feline Histiocytic Diseases

Cats have a narrower range of histiocytic proliferative diseases than dogs. Clear feline equivalents of cutaneous histiocytoma and the reactive histiocytes (CH and SH) have not been described. Cats are afflicted by the HS complex, and present with many of the same clinical syndromes as in dogs, including hemophagocytic HS. However, the incidence is much lower. Some injection site sarcomas in cats are reported to have a histiocytic appearance. The most common histiocytic disorder of cats is feline progressive histiocytosis (FPH), which has no canine equivalent. Cats present with skin lesions, which are solitary or multiple, non-pruritic, firm papules, nodules and plaques. Lesions have a predilection for feet, legs and face. FPH appears to follow a slowly progressive, indolent course, although terminal systemic involvement appears to occur. Therapy has been poorly studied for feline histiocytic disease in general; however, therapeutic recommendations as for dogs would seem appropriate.

References


