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Oncology **21**



MANAGING HISTIOCYTIC DISEASES Barbara E Kitchell DVM. PhD. DACVIM

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Canine histiocytic malignancies represent a group of neoplasms with shared morphological features but diverse cellular origin and potentially divergent biologic behavior.

The malignant histiocytic disease complex was first recognized in Bernese mountain dogs and it has been considered to be familial in this breed. Subsequently, improved

diagnostic techniques expanded the list of predisposed breeds to include flat coated retrievers, Rottweilers, and golden retrievers. The disease is characterized by proliferation and tissue infiltration of pleiomorphic histiocytic cells in multiple organs. Neoplastic histiocytic infiltrates are most often found in the spleen, liver, lung, bone marrow and lymph nodes, while atypical locations including ocular and central nervous system sites have been also documented. Canine histiocytic sarcoma may initially present as localized tumor or disseminated disease, but eventually widespread metastasis occurs with uniformly fatal outcome. Three distinct forms of the disease have been recognized based on the cellular origin of the tumor and the clinical course of the disease: histiocytic sarcoma, hemophagocytic histiocytic sarcoma, and periarticular histiocytic sarcoma.

Cellular origin

Normal histiocytes represent a subset of leukocytes that include monocytes, macrophages and dendritic antigen presenting cells (DAPCs) found in all tissues. These cells serve an integral role in the immune system. Histiocytes arise from bone marrow-derived CD34⁺ stem cell precursors, and under the influence of specific cytokines and growth factors differentiate to form cells of the monocyte/macrophage lineage or the dendritic cell lineage. As differentiated cells, macrophages and DAPCs share many of the same surface antigens, as well as surface receptors for immunoglobulin and complement molecules. Despite these similarities, enough morphologic, phenotypic and functional differences exist between them to allow categorization as different cell lineages.

Proliferative histiocytic diseases

Proliferative diseases of different DAPCs subpopulations have been documented in dogs. Canine cutaneous histiocytoma, a mostly benign self-limiting cutaneous epitheliotropic neoplasm, arises from proliferation of CD1⁺, CD11c⁺, Thy-¹⁻, CD4⁻ canine Langerhans cells. Canine reactive histiocytosis, which includes cutaneous and systemic forms, has been documented as an angiocentric, infiltration of CD1⁺, CD11c⁺, Thy-1⁺, CD4⁺ activated interstitial DAPCs. Clinical behavior and response to immunosuppressive therapy are consistent with other immunoregulatory disorders. As is seen in the human counterpart, localized and disseminated histiocytic sarcomas in dogs can mimic other spindle cell or round cell sarcomas.

Histiocytic sarcoma complex

Localized and disseminated forms of histiocytic sarcoma present with identical histopathological features. They manifest as poorly demarcated masses composed of proliferation of pleiomorphic, large, individualized round cells, or more densely packed bundles of plump spindle cells. The neoplastic cell population has a large amount of pale eosinophilic cytoplasm and large round to oval, indented or twisted, vesicular nuclei. Characteristic is the presence of large, round to stellate multinucleated giant cells. Mitotic rate is high and tumors contain areas of necrosis. The histiocytic sarcoma cell immunophenotype is CD1+, CD11c+, MHC II+, ICAM-1+, CD80+, CD86+, CD90+, consistent with that of DAPCs. Interstitial DAPCs, white pulp splenic DAPCs and other DAPCs may be the originators of these tumors. Hemophagocytic histiocytic sarcomas are characterized by a diffuse neoplastic expansion of the splenic red pulp zones by CD11d+, CD11c⁻, CD1⁻ histiocytes of macrophage type. The cells metastasize to the liver where they are first seen within the liver sinusoids and later form intrahepatic tumor masses. Localized histiocytic sarcoma lesions most often occur as a primary tumor involving the skin and subcutis of the extremities, although it may also be found in periarticular tissues surrounding large appendicular joints, or in spleen, lymph nodes, lung, or bone marrow.

Treatment of histiocytic sarcoma complex

A relative paucity of clinical studies describing the treatment of canine histiocytic sarcomas is available. Two recent clinical reports include a heterogeneous group of dogs suffering with localized, disseminated, and periarticular histiocytic sarcomas. Both reports include dogs treated in the adjuvant and gross disease setting, which makes the interpretation of results challenging. Responses to chemotherapy have been noted in dogs treated with lomustine, a nitrosourea chemotherapy agent in the alkylating drug class. Even after an initial response to chemotherapy, median survival times remain

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21 Oncology

in the 3- to 6-month range. In a recent multi-institutional study, lomustine was administered at a median dose of 70.8 mg/m² every 3-4 weeks for a median of 4 doses. The median survival time for the 59 dogs in this study was 106 days duration. In a different study, surgery as a single treatment modality did not significantly increase survival compared to no treatment at all. Dogs receiving any other type of therapy, whether radiation, chemotherapy, or multimodality treatment, lived significantly longer than dogs receiving only palliative therapy (167 versus 17 days).

There are a few reports of individual responses to chemotherapy with doxorubicin, liposomal doxorubicin, or paclitaxel. The most commonly used of these single agent therapies is doxorubicin (at standard dose of 30 mg/m² every 21 days by brief IV infusion), although some institutions favor the liposome encapsulated form of the drug. A dog with disseminated cutaneous histiocytic sarcoma that temporarily responded to multiple protocols, including chemotherapy with cyclophosphamide, vincristine, prednisone, mitoxantrone, dacarbazine, and etoposide, has been reported. We have had some success in treating metastatic histiocytic malignancies with a combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP protocol). While this protocol is a stardard one for the treatment of canine lymphomas, its use in histiocytic disease has been less common. This therapy consists of a rotation of doxorubin at 30 mg/m² IV on Day 1, cyclophosphamide orally at a dose of 50 mg/m² on Days 3, 4, 5, and 6 of Week 1, vincristine at a dose of 0.6 mg/m² IV on days 8 and 15, and prednisone at a dose of 20 mg/m² PO daily for week one, then every other day thereafter. This cycle is repeated on a 21 day basis, with dogs evaluated for CBC changes weekly and monitored for cardiac abnormalities by echocardiogram or electrocardiography before each successive dose of doxorubicin. We typically do not administer more than 6 cycles of this combination due to concerns for cumulative cardiomyopathic changes.

A case series study evaluated the treatment of dogs with HS with the human cytotoxic T-cell line TALL-104, which appeared to be beneficial to the 4 treated dogs. Insufficient clinical data and unavailability of the cell line make this treatment option practically irrelevant. Finally, most dogs are eventually euthanized at the time of diagnosis or tumor relapse because of poor clinical condition and poor prognosis.

Another line of therapy that is currently under investigation in veterinary medicine is the use of aminobisphosphonate medications, such as clodronate, alendronate, or pamidronate, to treat histiocytic sarcomas. The use of these types of drugs, which are typically used as bone sparing agents in osteoporosis in humans, is based on the observation that human Langerhan's cell histiocytosis has the potential to attain remission on these agents. We have seen responses in individual cases treated with pamidronate at 2 mg/kg IV infusion over 2 hours delivered on a monthly basis. Alternately, we have used alendronate (Foxamax) at a high loading dose of 70 mg/m² PO dayly for 14 days, then every other day for 14 days, then once weekly. Dogs receiving alendronate should be monitored for evidence of esophageal problems such as excessive ptyalism or regurgitation, as this drug has been reported to induce esophageal mucosal injury and even stricture in human patients who have retention of the pill within the esophageal lumen. Alendronate recently became available in a generic formulation, which has rendered bisphosphonate therapy much more economical for veterinary use.

Another agent that we have had limited experience using in the setting of histiocytic sarcomas is an antimetabolite agent called cladrabine. The dose we have employed is 0.063 mg/kg/day as a continuious IV infusion for up to a 5 day course. A CBC is evaluated at Day 3 of the infusion series, and if it is within normal limits the drug is continued for 2 additional days. Alternately, cladrabine may be administered at the same dose rate in TID divided subcutaneous doses for 5 days. This latter dosing approach appears to be less myelosuppressive than using the antimetabolite as an infusion, but is much more cost effective for veterinary patients. Validation of cladribine as an effective therapeutic agent for canine histiocytic disease is ongoing.

Future Directions

Currently, research efforts have been directed towards identifying histopathologic markers that accurately identify the cell of origin for each histiocytic disorder, and genetic defects underlying the disease. While the importance of histiocytic sarcoma genetic studies is evident, it is unlikely a genetic defect in the affected breeds would be easy to 'breed out'. Research to identify improved chemotherapeutic treatments for the disease will therefore continue to be of major importance.