

Therapeutic Management of Malignant Histiocytic Tumors: Innovative Approaches

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A combination taken from his article of the same title, by Rutteman, Teske, Spee, and Effert, along with my notes (Patricia Long)

Categories of Histiocytic Disease:

Reactive – considered immune disorders

- cutaneous histiocytosis (CH)
- systemic histiocytosis (SH) – more prevalent in BMDs

Neoplastic – disordered growth

- cutaneous histiocytoma (single or multiple)
- histiocytic sarcoma (HS)
 - o periarticular histiocytic sarcoma
 - o hemophagocytic histiocytic sarcoma (spleen)
 - o malignant histiocytosis (MH)

Histiocytoma

- there is a breed disposition, it is generally found in young animals age 3 months to 2 years. It is often found on the head (ear) and legs. It has a benign behavior and will often regress spontaneously.
 - Diagnosis is made by use of staining with antibody CD1.
 - Therapy
 - o Wait and see in young animals
 - o (cryo) surgery
 - o Corticosteroids – which may hamper immuno-mediated regression
 - o Radiotherapy
 - Prognosis is excellent in most cases. Still, In dogs > 3 years of age spontaneous regression may be rare, necessitating surgical removal. On the other hand, there are rare cases of multiple histiocytomas rapidly metastasizing, as in Langerhans cell in humans.
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Cutaneous Histiocytosis

- seen in young to middle age dogs
- single or multiple lesions
- lesions typically seen on the head, neck, extremities, scrotum
- waxes and wane, sometimes spontaneous regression is seen.

Systemic Histiocytosis

- seen in young typically male Bernese
- external lesions, but they can also be in other organs like spleen or liver.

These can be considered as one entity, reactive histiocytosis. They may be caused by immune system dysregulation, there has been no indication of infectious agents.

Histopathology is identical for CH and SH, with multiple infiltrates in the dermis (the inner layer of skin with all the blood vessels) and the panniculus (the dense fatty tissue). SH can be more lymphohistiocytic.

It is difficult to identify with pathology, specific stains must be used – CD1b, Thy01, CD4 (multiple markers). It is necessary to rule out granulomas, cutaneous lymphoma, and mastocytoma (mast cell). Clinical manifestation and expert histopathology are key for diagnosis.

Treatment relies on systemic immunosuppressants such as cyclosporine A and leflunomide. But a complication of such a treatment is that immune suppression leads to infection, or even - in the long term - that it may give rise to sarcoma.

Histiosarcoma Complex

Localized

Localized HS is locally invasive, found in soft tissue often near the joints, found typically in the extremities, but it may metastasize. Some classification systems call this histiocytic sarcoma, others refer to it as malignant fibrous histiocytoma. While these names may or may not be the same disease, they are often grouped together. Even if the primary tumor is removed (often involving amputation of the affected leg), most animals will develop metastases within one year, with regional lymph nodes, the lungs, liver and/or spleen the most frequently involved (Craig et al, 2002). Flat Coated Retrievers and to a lesser extent BMDs, and at a moderate level Rottweilers are all at increased risk (Morris et al, 2000).

Disseminated

If malignant tumors develop from histiocytes in internal organs (spleen, liver, bone marrow, lungs), the primary tumor can often not be identified. Affected animals often develop anorexia, major weight loss, anemia, and

sometimes fever. Masses in either or all of these organs (and sometimes in other organs such as the kidneys or central nervous system) can in the majority of affected dogs be detected by skilled radiography and/or ultrasound (Rosin et al, 1986, Schmidt et al, 1993). This manifestation is known by the name malignant histiocytosis (MH) or disseminated histiocytic sarcoma of cryptic (hidden) sites (Affolter and Moore, 2002).

Diagnosis:

- blood analysis
 - o anemia – frequently regenerative, most are Coombs negative
 - o rarely leukemic
 - o sometimes hypercalcemia
 - o sometimes liver dysfunction
- x-ray of the thorax – about 50% show lung masses
- ultrasound of the abdomen – about 50% have alteration of liver and/or spleen
- bone marrow cytology/histology – about 10 – 20% have tumor positive cytology

The immunohistochemistry for HS and MH are the same, but they are both different from histiocytoma and reactive histiocytosis. In Bernese, the disease is already widespread at diagnosis.

Early investigation on tumor type distribution in BMD based on cytology and/or histology, without the use of immune markers. At that time SH was grouped with MH, under the assumption of a shared pathogenesis:

BMD Cancer Predisposition, University of Utrecht, 1992 – 1997

600 tumors, 394 with completed information

Emphasis on malignant disease:

Sarcoma	43
MH/SH	76
Lymphoma	73
Mast cell	48
Carcinoma	23

Recent study based upon material in histopathology archives, in cases with doubt use of immune markers added:

Tumors in the BMD at Pathology archives from Utrecht University from 2000 – 2004

774 neoplasms

199 were histiocytic, or about 25.7%

Histiocytoma	68
CH	16

SH	36
CH/SH	4
HS	3
MH	41
HS/MH	4
SH/MH	15

On older reports there was frequently a mix-up in terminology.

Prognosis after diagnosis is poor. At the University of Utrecht in 16 dogs with confirmed MH, the average survival time was 4 months. Compare that to 11 dogs with CH/SN where the average survival time was 11 months. In France, 50 dogs with MH had an average survival time of 3 months with a median of 1 month.

Statistics from the United Kingdom for 38 dogs, average survival time:

Stage I, localized	9.5 months
Stage II, with metastasis	3 months
Stage III, true MH	0.5 months

Treatment of HS includes radical surgery and perhaps radiography. For disseminated HS normal chemotherapy has been unrewarding, and any benefits of experimentally treatments are unconfirmed.

Synovial tumors, survival:

After amputation, 10 dogs	5 months (range of 0.5 – 13 months)
After chemo, 4 dogs	3.5 months (range of 0.5 – 16)

Human treatment for Langerhans histiocytosis uses lomustine. This disease is rare in dogs. Treatment for MFH includes surgery, radiology, and chemotherapy. The role of chemo remains investigational.

In humans there is limited data on treatment for a special group of non-hodgkin's lymphoma using doxorubicin and vincristine, which indicated a complete response in 60 – 70%.

Recently administration of cultured cells from a human T-cell lymphoid cell line (TALL104) appeared to elicit anti-tumor activity in four dogs with 'MH.' Yet careful examination of clinico-pathological data indicates that three of these cases may instead have been affected by SH. The latter disease consists of histiocytic proliferations in the skin, without signs of true neoplasia, which often ulcerate, that at later stage may progress to involvement of lymph nodes, spleen and/or liver (Moore, 1986). This disease is currently seen as neo-neoplastic, but rather an immunological disorder with proliferation of dermal histiocytic cells (Affolter et al, 2000) – bad as may be – that finally (often in about one year) may lead to euthanasia. With recent advances in medical treatment, the disease may be brought under control for longer time.

When considering medical treatment of tumors, it should be recognized that the extent of the disease, in particular with MH, may have caused too much damage to vital organs (liver, bone marrow, kidney) which would exclude its application. Also, the greater the tumor mass, the smaller the chance to obtain a response.

In 10 dogs with HS/MFH/MH, after thoroughly informing the owners with respect to the uncertain outcome, medical treatment was attempted. With the sequential use of l-asparaginase, vincristine, cyclophosphamide / chlorambucil and doxorubicine and in some 5-fluorouracil, in some dogs not completed because of serious disease progression, none of these 10 cases experienced a positive response, defined as at least a 50% reduction of mass (= partial response) for at least 4 weeks. One dog had a short-lived response, but only for 2 weeks.

Innovative treatments to be examined:

- liposome-encapsulated cytostatics
- growth factor receptor kinase inhibition
- inhibition of causative gene(s)
- experimental drugs
 - o HU-1205 (endoperoxide sesquiterpene lactones)
 - Highly successful against human tumors in culture
 - Trial in The Netherlands, tested using 5 canine cell lines: (2) mammary tumors, (1) osteosarcoma, (1) bile duct epithelium, (1) kidney
 - With increasing doses it eliminated all viable cells
 - At high doses lethal in experimental beagles
 - A trial has just begun with dogs with HS/MH of limited extension, using intermediate doses

Nine of every ten new experimental treatments will fail. We need prospective treatments, and sharing.

Q & A:

Tessa Breen stated that the BMDs with disseminated HS last longer than the FCRs

Their pathologist is the head of the association.

Diagnosis is a problem if there is only one organ sample

If the disease is localized, they often just get the sample from the biopsy of the site and none later

If the samples are taken at necropsy, they may get more than one organ sampled

Dr. Rutteman cited Dr. Moore as the expert for classification of histiocytic

diseases, and thanked him for providing the insights gathered by him and his co-workers to the veterinary community.

Dr. Eckert stressed the need for a complete workup for accurate diagnosis:

Radiographs, ultrasound, abdominal biopsies, blood and serum chemistry