O – Oncology
RECENT ADVANCES IN MAST CELL TUMORS

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Very few tumors present in such a wide variety of clinical signs: they are indeed the great impostors! They can look like anything and behave differently depending on the histologic type, location and the extent of the disease. The following is a brief discussion about these tumors. Some highlights are as follows:

- Mast cell tumor granules do not stain well with Diff Quick type stains unless they are "soaked" in the alcohol for several minutes prior to staining.
- Some important prognostic indicators include duration of presence, location and histologic type in the dog.
- Mast cell tumors tend to metastasize to nodes, liver spleen and bone marrow...rarely to lungs.
- Radiation therapy is extremely effective for controlling local disease.
- Prednisone and vincristine when used as single agents induce a remission (partial or complete) in about 23% of the tumors.

Diagnostics

Diagnosis of mast cell tumors often can be made by a fine needle aspiration cytology but excisional biopsy is required if accurate histologic grading of the tumor is desired. Mast cell tumors are classified as round cell tumors along with lymphosarcoma, histiocytomas and transmissible venereal tumors.

Diagnostic workup of mast cells usually includes a number of procedures. These include a complete blood cell count (CBC), serum chemistry profile, and urinalysis. In addition, fine needle aspiration of the lesion, regional lymph nodes and examination of buffy coats or bone marrow helps to determine the extent of tumor involvement. A CBC is valuable in assessing animals with mast cell tumors because those animal patients with systemic mastocytosis occasionally have peripheral eosinophilia and basophilia in addition to circulating mast cells. Mastocytemia is a more common clinical phenomenon in the cat than in the dog. The CBC may also give evidence of gastrointestinal bleeding or gastrointestinal perforation. In general, mastocytosis associated with primary cutaneous tumors is more easily detected by examination of the buffy coat or bone marrow than by examination of peripheral blood. Care must be exercised in interpreting buffy coats since mastocytemia has been reported in a variety of acute inflammatory diseases of the dog including parvovirus infections. Peripheral mast cell counts may be high in cats with mastocytosis and have accounted for up to 25% of the total white cell count.

Therapy

Surgical considerations include wide surgical margins with at least 3 cm of normal looking skin around the tumor should be removed when possible. The 3 cm recommendation is a guideline and might not be feasible when the tumor is located on the face, lower limbs or in the inguinal region. It should be remembered that most mast cells extend laterally to adjacent tissue rather than deep into underlying muscles. All excised tumor should be examined histologically for the completeness of excision. Extension of the tumor beyond the surgical borders should prompt either wider excision or radiation therapy of the tumor bed. Approximately 50% of the mast cell tumors recur at the surgical site traditionally. Histologic grade is an important factor in predicting recurrence at the surgical site. Those that are undifferentiated tend to have a higher recurrence rate. Cats with mast cell tumors with splenic

involvement often will benefit from splenectomy. Survival times of 10 weeks to 30 months have been reported following splenectomy, even in patients with evidence of sytemic mastocytosis.

Seguin et al (J Am Vet Med Assoc 218[7]:1120-1123 2001) evaluated 60 mast cell tumors that were surgically excisted with cleanmarings in 55 dogs were included. Median follow-up time was 540 days. Three mast cell tumors recurred locally; median time to local recurrence was 62 days. Six dogs developed another mast cell tumor at a different cutaneous location; median time to a different location was 240 days. Three dogs developed metastases; median time to metastasis was 158 days. The authors concluded that additional local treatment may not be required after complete excision of grade-II mast cell tumors and that most dogs do not require systemic treatment.

Glucocorticoid therapy frequently results in partial or occasionally complete remissions in canine mast cell tumors. However, cats appear to be less responsive to glucocorticoid treatment. The effect of glucocorticoids is to reduce markedly the number of mast cells in the mast cell tumor. The exact mechanism by which glucocorticoids exert their cytotoxic effects on mast cell tumors is unknown although it may be similar to the effects of glucocorticoids on lymphocytes. The susceptibility of mast cell tumors might depend on the presence of intracytoplasmic glucocorticoid receptor sites. Glucocorticoid receptor sites have recently been found in the cytoplasm of canine mast cell tumors. Although sex steroid receptors for progesterone and estrogen have been recently described in dogs with canine mast cell tumors, the role of sex steroids in the treatment of canine mast cell tumors has yet to be investigated. The type of glucocorticoids administered appears to be unimportant but it has been suggested that intralesional corticosteroid may be more effective than systemic therapy for local disease. Fewer Cushingoid side effects have been seen with short-acting glucocorticoids such as prednisone or prednisolone when used in the dog. The usual dose of prednisone is .5 mg/kg orally administered once daily and that of triamcinolone is 1 mg for every cm diameter of tumor intralesionally, administered every two weeks. Remission times are usually 10 to 20 weeks. Dogs that are tumor free after six months however have a low incidence of recurrence and therefore therapy is usually discontinued at this time. Tumor resistance may be caused by the emergence of mast cells with fewer or ineffective glucocorticoid receptors. Survival data based on histologic grade correlates with various chemotherapeutic regimens has not been reported.

Vinblastine and prednisone or CCNU appear to be the most favored drug protocols for the treatment of mast cell tumors. The use of these drugs is always with surgery.

Rassnick and colleagues (J Vet Intern Med 13[6]:601-605 1999) evaluated the efficacy and toxicity of CCNU in 23 dogs with measurable mast cell tumors (MCT). Response could be evaluated in 19 dogs. Eight of the 19 dogs (42%) had a measurable response to CCNU. One dog had a durable complete response for 440 days. Seven dogs had a partial response for a median and mean duration of 77 days and 109 days, respectively (range, 21-254 days). The acute dose-limiting toxicity was neutropenia 7 days after administration of CCNU.

Thamm et al (J Vet Intern Med 13[5]:491-497 1999) evaluated 41 dogs with mast cell tumors treated with oral prednisone and vinblastine both in the adjuvant setting and in dogs with gross disease. Adverse effects were noted in 20% of the patients, usually after the 1st dosage. Median survival time (MST) for the entire patient population was not reached with a median follow-up of 573 days; however, the MST for dogs with grade 111 MCT was 331 days, with 45% of dogs alive at 1 and 2 years.

Ancillary drug therapy is important with canine mast cells. Animals with mastocytosis or palpable mast cell disease should receive H_2 antagonists. Cimetidine (Tagamet) reduced gastric acid reduction by competitive inhibition of the action of histamine on H_2 receptors of the gastric parietal cells. Ranitidine (Zantac, Glaxo Inc, Fort Lauderdale, FL), a newer H_2 antagonist that requires less frequent administration, is in some clinics. The objective of the therapy is to prevent gastrointestinal ulceration associated with elevated levels of histamine and to treat ulcers already present. Some new evidence indicates that cimetidine may also alter the immune response to this tumor as well as activation of certain alkylating agents. Dogs and cats with evidence of gastrointestinal ulceration and bleeding might also benefit from sucralfate (Karafate, Marion Labs Inc, Kansas City, MO) therapy. Sucralfate reacts with stomach acid to form a highly condensed viscous adherent paste-like substance that binds to the surface of both gastric and duodenal ulcer sites. The barrier formed at the ulcer site protects the ulcer from potential ulcerogenic properties of pepsin, acid and bile allowing the ulcer to heal.

Radiotherapy has been used alone or in combination with other treatment modalities. Most reports indicate remission rates of 48 to 77%. Doses of 3,000 to 4,000 rads were used in these studies. Total radiation therapy is usually fractionated and delivered over a period of

three to four weeks. The use of radiotherapy is somewhat expensive and is confined to referral centers. Mast cell tumors in regional lymph nodes and bone marrow appear to be more resistant to the effects of radiotherapy than those confined to the skin. Response of mast cell tumors to radiation therapy may correlate to histologic grade but has not been studied.

SUMMARY

Grade 1 Mast Cell Tumors

Dogs with grade 1 MCTs have a high likelihood of complete tumor control after complete surgical excision. A recent study showed that all grade 1 MCTs were completely excised with a 1-cm clinical margin. However, because tumor grading is performed histologically, not on cytology, all MCTs for which a grade is as yet uncertain should be excised for biopsy with wide (2 to 3 cm) margins.

Grade 2 Mast Cell Tumors

Three recent studies have challenged early assumptions[16,19] that dogs with grade 2 MCTs have a high likelihood of local recurrence even after apparently complete excision. These studies showed that with a more aggressive surgical technique and histology to examine margins (rather than the surgeon's clinical impression), dogs with grade 2 MCTs have a much lower rate of local recurrence and longer survival rates than previously reported. Specifically, between 5% and 10% of dogs had a local recurrence of MCT a median of 7 months after surgery (range: 2 to 24 months). More than 30% of these dogs had an MCT on the limb, for which some limbs were amputated. On the other hand, many of these dogs developed another MCT at a distant cutaneous site. These were considered to be de novo tumors (rather than cutaneous metastases, which have not been reported) and were diagnosed from 2 months to 4 years later, with a median time to diagnosis of about 1 year. Metastasis was rare, occurring in fewer than 3% of dogs.

Grade 3 Mast Cell Tumors

One study found that grade 3 tumors were more likely to be incompletely excised and more likely to metastasize than grade 1 or 2 MCTs. Radiation therapy is probably warranted (see below), and chemotherapy should be considered for grade 3 MCTs.

Prognosis

The natural behavior of mast cells suggests prognosis of this tumor depends on the species, breed, histologic grade, tumor location, clinical stage and growth rate. In general, cutaneous mast cell tumors carry a more guarded prognosis in the dog than in cat. Mast cell tumors in the boxer are usually of a lower histologic grade than when found in other breeds. Mast cell tumors in Siamese are of the less malignant histiocytic type. Histologic grade has been shown to correlate with survival following surgical excision by at least two investigators. The higher the histologic grade (more undifferentiated tumor), the poorer the prognosis. This criteria has not had universal acceptance however, probably due to the precise nature of histologic grading as well as tumor heterogeneity. Clinical staging and the extensiveness of microscopic tumor masses beyond what might be detected clinically also plays an important role in the failure of universal acceptance of the histologic grading system. In the cat, in addition to the histologic grading system described for the dog, the histiocytic mast cell variant tends to carry a better prognosis than the traditional mast cell. Tumor location is considered by many investigators to be an important prognostic feature. Tumors located in the perineal or preputial area are likely to metastasize both locally and to deep lymph nodes. Clinical stage is a clinical means of assessing tumor spread of the disease process. The higher the clinical stage, the more guarded the prognosis. A high histologic grade, however, should increase the clinical stage at least one level. Growth rate but not tumor size is determined also to be an important prognostic indicator. Growth rate reported by Bostock indicates that dogs that have tumors that grow greater than 1 cm per week have only a 25% chance of living an additional 30 weeks.

Reference

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