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TREATMENT OF MAST CELL TUMORS AND SOFT TISSUE SARCOMAS

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MAST CELL TUMORS

Mast cell tumors (MCT) are the most common cutaneous tumor in the dog and the 2nd most common in the cat. Older names for MCT include mast cell sarcoma and histiocytic mastocytoma. Mast cell tumor must be differentiated from mastocytosis, which is a systemic mast cell condition. Mastocytosis can be seen in animals with MCT but is not common. In people, mastocytosis is seen, whereas mast cell tumors are not. Mast cells are normal inflammatory cells containing a variety of bioactive compounds, which are partially responsible for clinical syndromes seen with MCT. Histamine and heparin are the major constituents and cause the typical metachromatic staining on Wright stains. Some anaplastic lesions will not stain well and in these cases, immunohistochemistry may be helpful. Heparin, as well as proteolytic enzymes, present in mast cells can be responsible for hemorrhage from the surgery site as well as delay in wound healing. Histamine can cause local or systemic allergic-type reactions as well as gastric ulceration.

Mast cell tumors have a wide range of biologic behaviors, which can be partially predicted by histologic grade. The standard grading scheme for MCT is divided into well differentiated (grade I), moderately differentiated (grade II) and undifferentiated (grade III). Grade I lesions are minimally invasive and do not metastasize. Grade II lesions are locally aggressive and invasive with a 10-20% rate of metastasis. Grade II lesions are locally invasive with a high (70-90%) rate of metastasis. Metastasis is typically to regional lymph nodes, liver, spleen or bone marrow.

Most MCT present as solitary masses. Low-grade tumors may be firm and have a lengthy duration. Higher-grade tumors may present with erythema, edema and/or ulceration. Manipulation of mast cell tumors can cause erythema and wheal formation (darius sign) following mast cell degranulation. Metastasis can present locally or regionally (lymph node) or can be disseminated, involving organomegaly and mastocytomia. A fine needle aspirate is usually diagnostic for MCT, unless the mass is anaplastic (undifferentiated). Tumor grade cannot be determined from cytology, but requires histology. Agrophilic nucleolar organizer regions (AgNORs) are an indirect measurement of nuclear activity and correlate with tumor grade. Although not a test performed by all laboratories, AgNORs have the advantage of being able to be performed on cytology, as well as histology specimens. Full staging of the patient presenting for MCT is indicated, unless it is known that the lesion is grade I. Aspiration of any enlarged lymph nodes, abdominal ultrasound with spleen and liver aspiration and a bone marrow aspirate are indicated. The discovery of systemic disease has a major impact on prognosis and can greatly alter treatment planning. Evaluation of the buffy coat for mast cells is a simple screening step to look for mastocytomia, however, false negatives exist and a bone marrow aspirate is preferred. Indicators of mastocytomia can also be noted on complete blood count if basophilia or eosinophilia is seen. Biopsy, prior to tumor resection is indicated for larger lesions, extremity lesions or those in

difficult locations. Tumor grade may well alter the treatment planning or the owner's willingness to treat in these cases. For small, trunk located lesions; an excisional biopsy may be reasonable if the need for re-resection (following incomplete initial resection) would not compromise the patient. In these cases, staging could be delayed until tumor grade is determined.

Surgical removal is the treatment of choice for local MCT disease. Grade II and III lesions warrant aggressive local resection, obtaining 3 cm lateral margins and one additional tissue margin deep to what the tumor touches. In certain areas, this type of resection will require some type of reconstructive procedure, or possibly a regional resection to be complete. Normal tissue margins should always be identified after removal so that the pathologist can assess the completeness of resection. In cases of incomplete resection, re-resection should be considered first if feasible. For re-resections, new margins are obtained as described above surrounding the old scar. Regional resection may also be re-considered. Complete surgical resection for dogs with no evidence of metastasis will result in upwards of 90% 1-year remission. For incomplete resection that is not amendable to surgery, radiation therapy to the site can be successful. Fractionated doses of approximately 50 Gy have resulted in 80-90% 1-year remissions.

For dogs with grade II tumors or evidence of metastatic disease, adjuvant chemotherapy should be considered. Although to date, no chemotherapy protocol has been proven efficacious, a combination protocol combining vinblastine, cytoxin and prednisone has shown some clinical responses. Previously evaluated drugs include cytoxin and vincristine, which were not shown to be efficacious alone. Responses have also been seen following the use of doxorubicin, mitoxantrone and L-asparaginase but are typically of short duration. Prednisone will consistently result in tumor response but the duration is short (30 days) and when used alone, it may induce drug resistance. Further evaluation of aggressive drug protocols may prove successful, however, to date, the overall survival for metastatic or grade III MCT is less than 6 months. Ancillary therapy for MCT may also be indicated, especially for disseminated disease. Histamine (H1 and/or H2) blockers are indicated for the prevention of allergic reactions and gastric ulceration. Gastrointestinal protectant agents may also be helpful in cases of suspected or confirmed ulceration.

Feline MCT generally behave in a less aggressive manner than in the canine. There are three distinct forms of MCT in the cat; mastocytic, histiocytic and visceral. The majority of cutaneous feline mast cells are mastocytic. Mastocytic MCT are further subtyped histologically into compact and diffuse. The most common subtype is diffuse, which behave very similarly to grade I MCT in the dog. Conservative surgical resection is generally curative. Diffuse mastocytic MCT tend to behave in a more aggressive manner, more similar to grade II or III MCT in the dog. Complete staging and aggressive treatment is indicated for the diffuse mastocytic form. Although the grading scheme for MCT in the dog does not apply to the cat, differentiation between compact and diffuse forms may help predict behavior and guide treatment planning.

Histocytic mast cell disease is most common in younger, Siamese cats. These cats usually present with multiple, inflamed, puritic lesions, which may actually spontaneously regress. This may be more of an allergic phenomenon than a true neoplasia. Biopsy is needed to differentiate this form

from the mastocytic form. The visceral form of feline MCT can present isolated to the spleen or intestine, or can be diffuse. Splenic MCT will present with vague signs and splenomegaly. Up to 50% will have bone marrow involvement and coagulation abnormalities are not uncommon. Up to 30% can present with abdominal effusions. Intestinal MCT does not usually present with mastocytosis, but will often have evidence of regional metastasis to lymph nodes, liver or peritoneum. For MCT isolated to the spleen or intestine, complete resection can result in a long-term (approximately 1-year) remission. Cases presenting with metastatic disease carry a much more guarded prognosis. Chemotherapy protocols similar to the dog are presently being evaluated for diffuse mastocytic disease or visceral MCT with evidence of metastasis.

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SOFT TISSUE SARCOMAS

Soft tissue sarcomas (STS) are mesenchymal tumors arising from connective tissue elements. They tend to occur in middle aged to older animals with a trend toward medium to large (dogs). There is no apparent breed or sex predilection. They can occur in any location with a prevalence for subcutaneous or muscle sites on the extremities or trunk. The most common histologic types include hemangiopericytoma (not cats), fibrosarcoma and neurofibrosarcoma. Some pathologists prefer to refer to all histologic types with a similar biologic behavior as STS. They are relatively slow growing yet locally invasive with a low rate of metastasis. Tumor grade, based on histologic features is predictive of local invasiveness and metastatic potential.^{1,2}

Case evaluation for cases of suspected STS ultimately involves a biopsy to confirm the diagnosis and for histologic grade for prognostication.^{3} Even if a specific numerical grade is not assigned by the pathologist, cytologic descriptions (differentiated vs undifferentiated) can give the surgeon a feel for potential behavior.^{4} Fine needle aspiration cytology should be performed to support the diagnosis of neoplasia and rule out tumors such as mast cell tumor.^{5} Cytology is often unrewarding in diagnosing STS since their connective tissue nature does not result in cell shedding in large numbers. A wedge biopsy is preferred to obtain adequate tissue for histologic assessment but multiple needle core biopsies can be adequate, especially for deep masses. Excisional biopsy should only be considered for very small lesions on the trunk when STS is suspected.^{3}

Assessment of degree of regional involvement is important for treatment planning in cases of STS. Regional radiographs, especially for extremity lesions will demonstrate bony involvement which is essential to know since removal of the effected bone (amputation, rib resection) is required for disease control in these cases. Additional imaging modalities such as ultrasound, CT or MRI can be helpful to differentiate tissue interfaces or involvement of vital structures. Any and all enlarged lymph nodes in the region should be aspirated or biopsied to evaluate for regional spread. Although thoracic metastasis evaluation is of low yield in cases of STS, due to the low rate of metastasis, it is still a recommended preoperative evaluation tool since presence of metastatic disease may well alter the prognosis and treatment plan significantly.^{6}

Planning of the surgical resection and closure of the wound is based on the location, size and potentially the grade of the mass. Since all various histologic types that fit in the category of STS have similar biologic behavior, histologic type has little bearing on planning of tumor resection. Available treatment options include surgery alone, surgery followed with external beam radiotherapy and surgery followed by chemotherapy.^{6}

Surgery is the preferred treatment option and with adequate pre-treatment planning and strict attention to principles during resection can result in better than 80% long term disease control with a high potential of cure.^{7,8} Wide surgical margins are necessary for complete macroscopic and microscopic resection. Two to three centimeters around the mass in all planes is a target goal and is somewhat dependent on location and the proximity of vital structures. Soft tissue sarcomas will often appear to be encapsulated and this can tempt the uninitiated surgeon into 'peeling the mass out'. These tumors tend to have a pseudocapsule rather than a true capsule. This pseudocapsule is most often comprised of compressed tumor cells and marginal (peel-out) surgeries will invariably be incomplete. Deep margins are often the most deceiving with STS and it is recommended to remove at least one additional tissue plane beyond those tissues that are in contact with the tumor. Such 'radical resection is often more feasible on the trunk. Wide margins on the extremities may require special closure techniques or may not be feasible without amputation. Limb amputation for the treatment of STS should not necessarily be considered a last resort as better than 90% of all animals will have good function following the surgery and the majority can look toward cure with STS disease treated by amputation.^{7-12}

Once a tumor is resected, it is important not to assume the resection is complete, even with radical margins. Margins of interest should be identified for pathologic evaluation. Decide where the resection was closest to the tumor and mark this margin. Additional margins to consider would be deep, lateral and a skin margin if a subcutaneous tumor. Areolar tissue margins are difficult to access since they are easily distorted and tend to shrink rapidly on fixation giving the marked margins the appearance of being right on the tumor despite a wide margin. If the resected specimen is large, it can be partially 'loafed' to allow fixation. It may help to draw a picture of the specimen and label margins for future reference and to allow the pathologist to better chose sampling regions. If margin evaluation is essential to the case, then the entire specimen should be fixed, even if only sections are initially submitted. If the interpretation is then in question the remainder of the specimen can be utilized.^{4,13}

Once histologic margins have been reported, it becomes the surgeons task to interpret the results. If there is any question as to the report, it may help to review the specimen with the pathologist to discuss how the sections were cut in. This will help the pathologist as to orientation of the surgical margins of interest.^{14} A report of clean margins (tumor does not extend to marked margins) must be interpreted with caution. It is not feasible for a veterinary pathologist to cut and mount an entire resected specimen unless it is quite small. Therefore, he or she must take what is felt to be representative samples. This is where accurate descriptions and margin identification can be an invaluable aid. It is still possible, despite our combined best efforts that incomplete margins can be missed. A report describing "no tumor was found" also falls into the category of 'interpret with caution'. This often occurs when re-resection is performed for

incomplete margins. This can also occur if a large incisional or excisional biopsy is performed and the entire tumor removed.

Occasionally a report will describe tumor cells extending to within a few cell widths of a marked margin. Considering this a complete margin is highly dependent on the tumor grade. Such a margin may be adequate with low grade but must be suspect for high grade STS

An incomplete margin, no matter where it might be located in reference to the mass must always be interpreted as an incomplete resection. A histologically incomplete margin for a STS will invariably result in local recurrence.^{7} Again, if in doubt, review the specimen with the pathologist. It must be assumed that if the tumor was cut through at any level during resection that the entire wound is potentially contaminated. This requires treatment of the entire previous wound if re-resection or adjuvant therapy is elected.

If resection margins are incomplete, re-resection of the lesion should be considered first, if the original resection was in a location allowing new wide margins. Margin goals are still the same and since the entire previous wound must be considered contaminated, the new margins must be around the entire previous wound. Re-examination of the new resected margins should likewise be performed.

If resection margins are incomplete and it is suspected that only microscopic disease remains in the patient (no bulky disease), external beam radiation therapy can be considered adjuvantly.^{15-17} Megavoltage radiation of a STS would be containing microscopic disease has been shown to result in a 70-80% control rate at one year in veterinary patients. Side effects to the radiation in the majority of these patients is relatively superficial (confined to the skin) and transient. Certainly each case must be approached on an individual basis. For STS that are not amenable to wide local resection or if radical surgery is not favored by the owner, marginal resection of the mass and adjuvant radiation therapy could be planned from the treatment outset. Radiation therapy for bulky disease has resulted in marginal success.^{18}

Chemotherapy for bulky disease has not been shown to be highly effective in cases of STS.^{19} Therefore, chemotherapy cannot be considered a good option for initial therapy planning. Chemotherapy for microscopic disease (after marginal or incomplete resections) has not been completely evaluated for veterinary patients. Cisplatin has shown efficacy against a variety of sarcomas and could be considered for adjuvant therapy for STS. Other drugs that could be considered might include doxorubicin, mitoxantrone and taxol.^{20} None of these drugs is well proven for treatment of STS in animals but could be considered on a case by case basis.

We have treated 30 STS patients using intracavitary cisplatin released from a biodegradable polymer with preliminary local disease control similar to that of marginal resection and radiation therapy.^{21} A porous biodegradable solid polymer termed **Open cell PolyLactic Acid** which is (OPLA^a) impregnated with cisPlatin (OPLA-Pt) is placed within the wound following a marginal resection and prior to wound closure. This 'intracavitary therapy' results in cisplatin concentrations within the wound cavity which far exceed those obtainable with intravenous administration without high systemic concentrations which would result in toxicity. It is felt that such intracavitary therapy is effective treatment for microscopic disease left behind following incomplete resection. Fifty percent of our study population developed local tissue reaction to the platinum/polymer combination with

15 % requiring removal of the implant. We are presently investigating a third generation injectable polymer for similar use in the hope that we can decrease this local toxicity. Other drugs may be potentially used for intracavitary therapy of STS as well. This method may prove effective, allowing limb salvage options on extremity masses without having to rely solely on adjuvant radiation. Longer follow-up and additional case accrual is needed before definitive conclusions can be made.

Re-evaluation of STS patients after treatment focuses on local recurrence of disease.^{6} Physical examinations with careful palpation of the tumor site is paramount, with biopsy of suspected areas. Recurrent tumors tend to have more aggressive biologic behavior than the original mass, showing more rapid growth and possible increased tissue invasion and metastatic potential. Options for treatment of recurrence are similar to those for the primary lesion. If, however, aggressive therapy was performed on the primary mass and local recurrence resulted, even more aggressive secondary therapy must be considered. Grade of the recurrent mass may help guide therapy.^{4} Metastasis evaluation might be recommended on a 6 month basis, dependent somewhat on tumor grade.

Proper treatment planning for STS based on knowledge of typical biologic behavior as well as expected behavior (grade) is essential with familiarity with all potential treatment options. Proper postoperative assessment and follow-up is vital for monitoring disease control and prompt treatment of uncontrolled disease. Soft tissue sarcomas can be a frustrating disease to treat, but adherence to solid surgical oncology principles can greatly increase the odds of good disease control.

Footnotes: ^a OPLA, THM Biomedical, Duluth, MN

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