Canine and feline cutaneous mast cell tumours: a clinical update

Mast cells tumours are the most common malignant skin tumours in the dog and rank among the three most common feline cutaneous malignancies.

The biology of mast cells
Mast cells are found throughout the body but are most numerous in the skin and the vascularised submucosa of the gut and respiratory tract. Mast cells are of mesenchymal origin. Undifferentiated precursor cells, of bone marrow origin, migrate through vascular walls and differentiate in situ. The lifespan of mast cells is of the order of months. Cutaneous mast cells are located in the dermis and hypodermis. In response to stimulation, mast cells may migrate subepidermally in the dog and into the epidermis of the cat.

Mast cells are an important part of the skin immune system (SIS). They play an important role in the production of inflammatory mediators. They also play an important part in the regulation of wound healing. Main trigger for mast cell activation/degranulation is crosslinking of surface bound IgE. Other triggers include:
- Neuropeptides from nerve endings (e.g. substance-P)
- Histamine releasing factors and interleukin-1 from inflammatory cells
- Cytokines and thrombin from vascular endothelium
- Complement
- Feedback from fibroblast cytokines
- Physical irritants

Mast cells produce pre-formed and synthesised mediators. Pre-formed products are located within the mast cell granules and are ready for immediate release. Synthesised factors are one of the major mechanisms of late-phase inflammatory reactions. Heparin, a synthesised mast cell product, is important for inhibition of clotting once injured blood vessels have been sealed.

Based on the types of enzymes produced, it is thought there are different populations of mast cells. It is not clear if this has some relation to the difference in behaviour of mast cell tumours.

Table I – Mast cell mediators
- Histamine and other vasoactive amines
- Chemotactic factors
- Heparin
- Multiple interleukins and other cytokines that recruit and stimulate T-cells, granulocytes and macrophages
  (for example, interleukins, interferon-γ, tumour necrosis factor-α, inflammatory eicosanoids (prostaglandins, leukotrienes, thromboxanes)
- Proteolytic enzymes
- Platelet activation factors
- Tissue growth factors

Clinical presentation
The average age of canine mast cell tumours (MCTs) is eight years. An Australian study has indicated a higher incidence in Caninae cutaneous and feline mast cell tumours than other breeds. MCTs are also commonly recognised in labradors and terrier breeds. In the shar pei, MCTs may be seen in dogs as young as one year of age (figure 5). It is vital to understand that MCTs can look like any type of cutaneous nodule or subcutaneous mass. Subcutaneous MCTs can look and feel like lipomas. Note the variations in presentation in figures 2-5. Clients should be offered the option of a fine needle aspirate in all cases of a skin nodule or a subcutaneous lump. Failure to offer this test to clients leaves the clinician liable to accusations of negligence if the “lipoma” or plasma containing basophilic granules that obscures much of the nucleus (figure 1). In cytology specimens, mast cells appear as individual cells (rather than in sheets) and are often associated with a variable number of eosinophils. Malignant mast cells are fragile and there may be many free mast cell granules visible between cells in the sample. These free granules need to be differentiated from bacteria and contamination found in old solutions of stains.

Several authors state that mast cell granules may not stain properly with Diff-Quik, a modified Romanowsky stain. Slides need to be left in the fixer for at least two minutes before using the colour stains. In some cases, the mast cell granules may fail to stain at all.

In cases where the fine needle aspirate is dubious or where pre-surgical planning, a pre-surgical fine incisional biopsy is recommended. During
biopsy of manipulation of MCTs, mast cells mediators may cause hypotensive shock. These reactions are relatively infrequent but patients should be premeditated with an H1 antihista- mune such as diphenhydramine or chlorphen- ramine prior to biopsy or surgery.

The differential diagnosis of MCT includes: inflammatory tissue, cutaneous histiocytosis and other round cell tumours (histiocytoma, cuta- neous lymphoma, plasmacytoma, transmissible venereal tumour and malignant histiocytosis).

Some cases of melanoma (melanotic and ane- plastic) may have a cytological pattern consis- tent with a round cell pattern. If the fine needle aspirate is inconclusive, a presurgical incisional biopsy is indicated. In the case of poorly differen- tiated tumours, immune/hi stochemical staining to eliminate the other differentials but is not diagnostic in all cases. Mast cells can be identi- fied using toluidine blue and stain positively for proteolytic enzymes such as chymase and tryptase but may lose this property if poorly differentiated. Histo cytoses can be identified using MHC II; CD3 for T lymphocytes and CD79a for B lymphocytes and plasma cells.

The excised tumour, to assist with staging, prog- nosis and decisions on adjunct chemotherapy. Hepato/splenomegaly, as determined by palpation, radiography and ultrasound, is suggestive of metastasis. This may be confirmed by ultrasound guided biopsy. Paraneoplastic histamine induced gastric/duodenal ulceration may be evident as vomiting +/- blood and the presence of blood in the stools. The blood per- oxidase tests, commonly used to detect occult faecal blood, are very sensitive to dietary blood. The patient should be placed on a meat free diet for three days before testing. Haematology may reveal a regenerative anaemia and other signs of blood loss in the case of gastro/duodenal ulcer- ation or in the uncommon case of heparin- induced coagulopathy.

**Therapy of canine mast cell tumours**

Surgery

Excision by ‘cold steel’ surgery remains the treatment of choice. Cryosurgery, radiosurgery and laser surgery are used but there have not been published data to demonstrate their supe- riority or otherwise in canine MCTs with respect to standard surgery. The optimal surgical margin for grade I-II MCTs has been accepted to be 2- 3cm. Simpson et al, 2004 that suggest “a 2 cm lateral margin and a deep margin of 1 fascial plane appear to be adequate for complete exci- sion of grade I-II MCTs in dogs”. The optimi- mum excision margin for grade III tumours has not been established. The clinician need to evalu- ate each case based on the criteria discussed under prognosis. Optimum surgical results are achieved where the clinician has diagnosed the tumour by fine needle aspirate, gr aded the tumour through histopathology of an incisional biopsy and staged the patient by a complete physical, laboratory and imaging examination. Proper planning reduces the likelihood a second surgery to remove ‘contaminated’ margins.

Within the limitations of the study, the findings by Michels et al, 2002, indicate that surgery on grade II-III MCTs may be of benefit even if the optimum surgical margins can not be achieved. Premedication with an H1 antagonist antihistamine is advisable to reduce the risk of shock caused by the release of histamine. Once the histamine is bound to H1 receptors, antihista- mines do not displace it. Malignant mast cells tend to produce less heparin than normal ones, however a clotting profile before surgery is to be encouraged, especially in cases where extensive resection is required. Prior to surgery, MCTs can be reduced in size by using intra-tumour triamcinolone at a dose rate of 1.0 mg/cm tumour diameter, repeated at 2 weekly intervals.

In general, surgery is not indicated for dogs with extensive metastasis. These dogs need to be palliated with chemotherapy and control of the paraneoplastic symptoms.

**Chemotherapy**

Chemotherapy, according to most authors, is not indicated in cases of fully excised grade I-II MCTs where staging has eliminated spread to the local lymph node or beyond. Prednisolone alone (1mg/kg SID) has a low success rate. McCaw et al, 1997 demonstrated a 20% response in a group of dogs with grade II-III MCTs. Only one dog achieved complete remission. Vinblastine and melphalan in combination have been shown to be effective. Davies et al, 2004 reported on 27 dogs with inadequately excised MCTs treated with the combination. After 12 months, 52 per cent were free of MCT. “There was no confirmed tumour-related mortality. Although toxicity from the chemotherapy was generally mild, one dog died of sepsis during treatment.” Thanum et al, 1999 reported on two groups of dogs: one group with gross disease and another with incomplete resection. They reported a 47 per cent response rate in the gross disease group (71 per cent of these responses were complete).

As adjuvant therapy to incomplete surgical resec- tion, the authors reported a 57 per cent 1- and 2year disease-free rate. Median survival time for dogs with grade III MCT was 331 days. Indicative dose rates are: prednisolone 2mg/kg SID, gradually reduced and discontinued after 5-6 months, plus vinblastine 2mg/m2 every 4 weeks then fortnightly for a further 4 treatments. A haematological and biochemical profile should be performed before each administra- tion of vinblastine. Couto, 2003 incorporates an alkylating agent in this protocol using cyclophos- phamide 50mg/m2 orally every 48 hrs or 4 times weekly. To prevent haemorrhagic cystitis chloram- bucil is substituted for cyclophosphamide after 8-12 weeks of treatment.

Thamn et al, 1999 evaluated the response CCNU (lomustine) in 19 dogs with cutaneous MCT. Eight of the 19 dogs (42 per cent) had a measurable response to CCNU. Only 1 dog had a durable complete response and seven dogs (37 per cent) had a partial response with a median and mean duration of 77 days and 109 days, respectively (range: 21-254 days). In this series, the dose rate of CCNU used was 90mg/m2 oral- ly every 3 weeks. Other indicative dose rates vary from 50-100mg/m2 every 3 weeks. The main side effect is an acute dose-limiting neutropaenia, occurring 7 days after dosing. Kristal et al, 2004 reported severe and potentially fatal cumulative hepatotoxicity in over 6% of dogs treated with CCNU. Couto, 2003 combines CCNU with prednisone (40-50 mg/m2 SID for 1 week then 20-50mg/m2 EOD).

Before beginning chemotherapy, the clinician needs to be aware of the patient monitoring and human safety issues associated with the agents used.

**Radiation and other therapy**

Radiation therapy has a high rate of success as adjunct therapy to incompletely removed grade I-II MCTs. Hahn et al, 2004 reported a 97 per cent cell remission rate of 65 per cent and 71% survival rate 1 year after radiation treatment of incompletely resected grade III MCTs. Radiation therapy requires multiple doses and is limited to specialised institutions.

The use of local deionised water injections was advocated in the early 1990s and this procedure has subsequently been discredited by Jaffe, 2000.

Trials with tyrosine kinase inhibitors in the treatment of canine MCTs are under way and are yielding positive results (see prognosis). There is some limited data to suggest photodynamic therapy (treatment with a photosensitizing agent then exposure to appropriate light) offers...
benefits in the treatment of inoperable superficial canine MCTs. Diets low in carbohydrates and high in protein and fats, especially omega-3 oils, may be of benefits in the management of canine neoplasia in general. There are currently no published data available on the benefits of dietary management of canine MCTs. Canine MCTs do not express cyclooxygenase-2 (COX-2) in any appreciable fashion (unlike many canine epithelial tumours). This, theoretically, reduces the potential benefit of COX-2 inhibitor therapy in canine MCTs.

In the case of systemic paraneoplastic mast cell disease the following agents are of value:

- H1 antagonists such as chlorpheniramine or diphenhydramine to counter the inflammatory effects of histamine.
- H2 antagonists to control gastric ulceration. Cimetidine has (anecdotally) been described to produce a protective adherent coating over the mucosa of dogs, and local tumour recurrence developed in 62 per cent of dogs, and local tumour recurrence developed in 62 per cent of dogs, whereas in many neoplastic mast cells KIT accumulates in the cytoplasm, primarily adjacent to the nucleus. A correlation between the expression of the KIT receptor and the histologic grade of MCTs has been made. CD10-positive, CD3-positive, and Ki67-positive cells are the most appropriate internal control.

Vitamin E has been shown to stabilize mast cells, predominantly on the cell membrane, and to exert a protective effect against histone damage. Vitamin E at a dose of 200 mg/day was administered to 97 dogs with mast cell tumours. The results showed a significant decrease in the number of mast cells with histone damage in the treated group compared with the control group.
The presentation is consists of single or multiple nodules or areas of plaque, often involving the head. Pruritus, erosion or ulceration may be present. Subcutaneous mast cell tumours are uncommon in cats (as distinct from dogs). Eosinophils are not a common feature of the cytology of feline MCTs.

There are no established chemotherapy protocols for feline MCTs. Couto, 2003 advocates prednisolone (48 mg/kg SID or EOD) and, if required, chlorambucil (20mg/m² every 2 weeks).

Urticaria pigmentosa is a syndrome characterized by a papular reaction in young Devon Rex or Sphinx cats. The papules contain an infiltrate of mast cells and eosinophils. The feline syndrome is not a neoplastic mast cell disease, but rather the name is based on a similarly-presented human disease. A significant proportion of cases will respond to prednisolone and/or essential fatty acid therapy but tend to relapse when treatment is discontinued. It is most likely that this condition is breed-specific hypersensitivity reaction pattern, similar to feline eosinophilic plaque or eosinophilic granuloma, rather than a reaction pattern, similar to feline eosinophilic plaque or eosinophilicgranuloma. The presentation is consists of single or multiple nodules or areas of plaque, often involving the head. Pruritus, erosion or ulceration may be present. Subcutaneous mast cell tumours are uncommon in cats (as distinct from dogs). Eosinophils are not a common feature of the cytology of feline MCTs.

Histological grade Grade I good prognosis, Grade III poor prognosis. Grade II see text

Rapid growth and/or ulceration Prognosis poorer

AgNOR counts, C-KIT mutations and PCNA counts Correlated to relapse. Not yet commercially available in Australia.

Stage, Spread to local lymph node and beyond Prognosis poorer

Paraneoplastic systemic signs Prognosis poorer

Location Limb extremities, on the muzzle and in association with mucocutaneous sites poorer prognosis. Inginal or perineal region, see text

Breed and age of onset Variable data

Tumour cells at surgical margins Prognosis, especially longer term, poorer, see text

Multiple tumours Prognosis more guarded.

Cutaneous nodule, subcutaneous MCT or tumour depth. No difference

Summary - Any cutaneous nodule or subcutaneous mass is potentially a mast cell tumour until proven otherwise.

- Surgery is the treatment of choice for all MCTs without metastasis to the viscera.

- Optimum surgical results are achieved where the clinician has diagnosed the tumour by fine needle aspirate, graded the tumour through histopathology of an incisional biopsy and staged the patient by a complete physical, laboratory and imaging examination.

- The main prognostic factor in dogs is histological grade. Other prognostic factors are listed in Table II and discussed in the text.

- The prognosis for a completely-removed grade I MCT is good. All grade III MCTs have a guarded prognosis even if completely removed.

- The prognosis for a grade II MCT, without evidence of systemic spread is generally good, however a percentage will relapse locally or metastasise (dogs).

- The prognosis for a canine grade II MCT, where histologically clean surgical margins can not be obtained, is not hopeless.

- Adjunct chemotherapy is indicated in cases of systemic spread of MCTs, incompletely removed grade II MCTs and all grade III MCTs. (dogs)

- Radiation therapy (if available) is valuable in the case of grade III MCTs and incompletely removed grade I-H MCTs (dogs).

- Feline MCTs have a different signalment, presentation and prognosis to that of dogs.

- The grading system that applies to canine MCTs is not prognostic in cats.

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Figure 4 - Subcutaneous grade III MCT on the shoulder of a 7 year old Labrador. The mass had spread to the pre-scapular lymph node at the time of presentation. Courtesy of Dr Stefaan Van Poucke.

Table II – Factors affecting the prognosis of canine MCTs

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