Canine and feline cutaneous mast cell tumours: a clinical update

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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 submucosae 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 life span 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). The main function of mast cells is 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, granuloctes and macrophages (for example, interleukins, interferon-_, tumour necrosis factor- _) Inflammatory eicosanoids (prostaglandins, leukotrienes, thromboxanes)
- Proteolytic enzymes
- Platelet activation factors
- Tissue growth factors.

CANINE MAST CELL TUMOURS

Clinical presentation

The average age of canine mast cell tumours (MCTs) is eight years. An Australian study has indicated boxers, australian cattle dogs and staffordshire bull terriers were at significantly greater risk of developing 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 "wart" later turns out to be a mast cell tumour. Most canine MCTs present as solitary lumps but multiple masses are seen in 10-15 per cent of canine MCT cases (figure 3).

Some cases of MCT may present with Darier's sign (figure 5); oedema and inflammation associated with the local production and release of mast cell mediators. Cases may present with pruritus, caused by the local effects of mast cell mediators. Paraneoplastic signs may be seen if there has been metastasis or significant local production of mast cell products. These signs include melaena and vomiting caused by gastric ulceration or coagulopathy (very occasionally) due to heparin release. Haematology may be normal or show eosinophilia, neutrophilia or anaemia (due to gastro-intestinal haemorrhage). Mostly, serum biochemistry is normal except in some cases of extensive metastasis and lowered albumen in cases of severe/chronic haemorrhage.

Diagnosis

Fine needle aspirate is sufficient to establish a diagnosis in 90+ per cent of cases. In normal tissue, mast cells should be no more than 1 per cent of cells identified and there should be less than 1 mast cell per high power field (HPF). Inflammatory tissue may contain 1-5 mast cells per HPF (10 per cent of cells). In the case of MCTs, over 50 per cent of the cells identified should be mast cells and there may be accompanying eosinophils and neutrophils, attracted to the mast cell chemotactic factors.

Mast cells are classified cytologically as round cells. A round cell pattern in a cytological specimen includes the following features:

- Round to oval shaped cells (as distinct from the spindle cell pattern)
- Discrete cells (rather than in sheets or clumps as in the epithelial pattern)
- The round cell is the dominant cell in the specimen

Individual mast cells typically contain a round to oval nucleus with cytoplasm 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 solution 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 grading is desired in procedure planning, a pre-surgical fine incisional biopsy is recommended. During

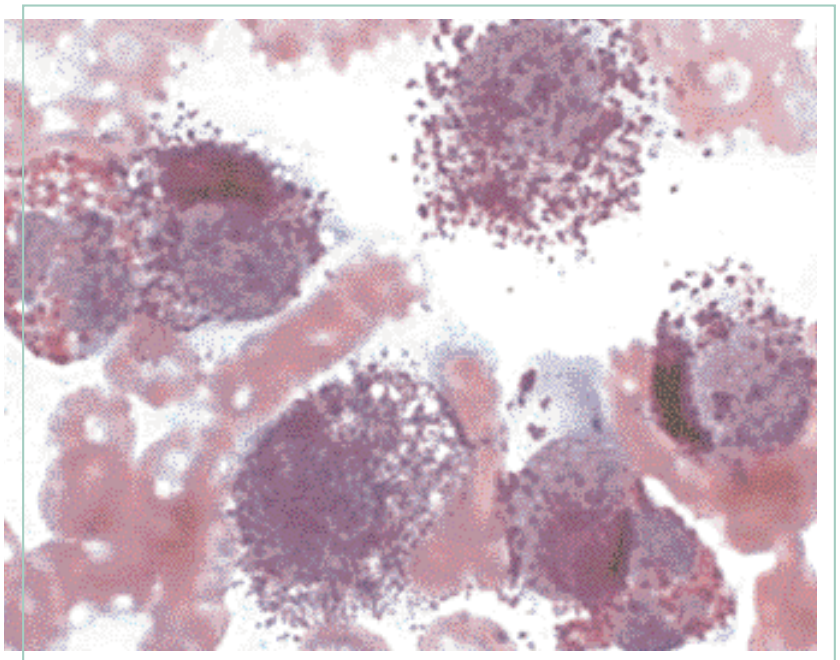

Figure 1 - Canine MCT: typical fine needle aspirate cytology. Note the eosinophil at 9 0'clock. ***Courtesy of Dr Ken Latimer.***

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 antihistamine such as diphenhydramine or chlorpheniramine prior to biopsy or surgery.

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

Some cases of melanoma (melanotic and amelanotic) may have a cytological pattern consistent with a round cell pattern. If the fine needle aspirate is inconclusive, a pre-surgical incisional biopsy is indicated. In the case of poorly differentiated tumours, immuno/histochemical staining to eliminate the other differentials but is not diagnostic in all cases. Mast cells can be identified using toluidine blue and stain positively for proteolytic enzymes such as chymase and tryptase but may loose this property if poorly differentiated. Histiocytes can be identified using MHC II; CD3 for T lymphocytes and CD79a for B lymphocytes and plasma cells.

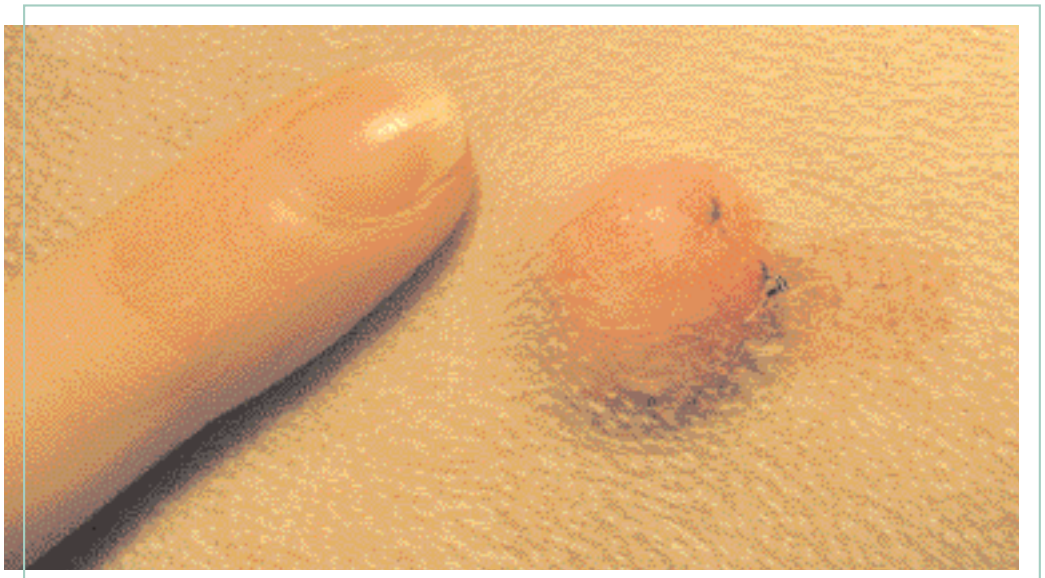

Figure 2 - A grade II MCT on the flank of an eight year old terrier with a "button tumour" appearance, grossly resembling a histiocytoma.

Grading of MCTs can not be performed from fine needle aspirate cytology; this can only be done from an incisional or post surgical biopsy specimen examined histopathologically. The histological grading system of mast cell tumours (grades I-III), based on their differentiation and number of mitotic figures, was established by Patnaik et al (1984) and is still the most important prognostic indicator (see below).

Staging of mast cell tumours

Mast cell tumours spread by aggressive local invasion of tissue and by metastasis. Metastasis is usually via the regional lymph node to the liver, spleen, bone marrow , other lymph nodes and viscera. Metastasis to the lung is relativity rare. The regional lymph node should be examined by fine needle aspirate, even if it does not feel grossly enlarged. In cases of acute inflammation, regional lymph nodes may contain mast cells. In dubious cases, an incisional lymph node may need to be submitted for histopathology to determine if metastasis has occurred.

Mast cells in the peripheral circulation, as identified in buffy coat smears, may indicate metastasis but may also be the result of acute inflammation (more commonly in cats than dogs). In no way does a negative buffy coat smear rule out metastasis. The presence of mast cells in bone marrow smears is more specific for systemic spread of malignant mast cells. Post surgery, if possible, the local lymph node should be submitted for histopathology, together with the excised tumour, to assist with staging, prognosis 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 gastro/duodenal ulceration may be evident as vomiting +/- blood and the presence of blood in the stools. The blood peroxidase 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 ulceration 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 superiority 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 excision of grade-I and -II MCTs in dogs”. The optimum excision margin for grade III tumours has not been established. The clinician need to evaluate 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, graded 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 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 histamine is bound to H1 receptors, antihistamines 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 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, 1994 demonstrated a 20% response in a group of dogs with grade II-III MCTs. Only one dog achieved complete remission. Vinblastine and oral prednisolone in combination, has 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.” Thamm 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 resection, the authors reported a 57 per cent 1- and 2-year 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 3-6 months, plus vinblastine 2mg/m^2 IV weekly for 4 weeks then fortnightly for a further 4 treatments. A haematological and biochemical profile should be performed before each administration of vinblastine. Couto, 2003 incorporates an alkylating agent in this protocol using cyclophosphamide 50mg/m^2 orally every 48 hrs or 4 times weekly. To prevent haemoragic cystitis chlorambucil is substituted for cyclophosphamide after 8-12 weeks of treatment.

Thamm 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 for 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/m^2 orally every 3 weeks. Other indicative dose rates vary from 50-100mg/m^2 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 20-25mg/m^2 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 an overall 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. This painful 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

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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 benefit 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 cyclooxigenase-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 have positive immunomodulation activity. Newer H2 antagonists such as famotidine require less frequent administration.
- Sucralfate reacts with gastric secretions to produce a protective adherent coating over gastric and duodenal ulcers.
- Antacids are of value, especially in combination with H2 antagonists.
- The use of cyproheptadine, an anti-serotonin (5-HT) agent, is controversial as there is doubt about the capacity of canine mast cells to produce 5-HT.
- Vitamin E has been shown to stabilize mast cells in vitro. Doses of the order of 400-800 IU/patient BID may be of value (unproven).

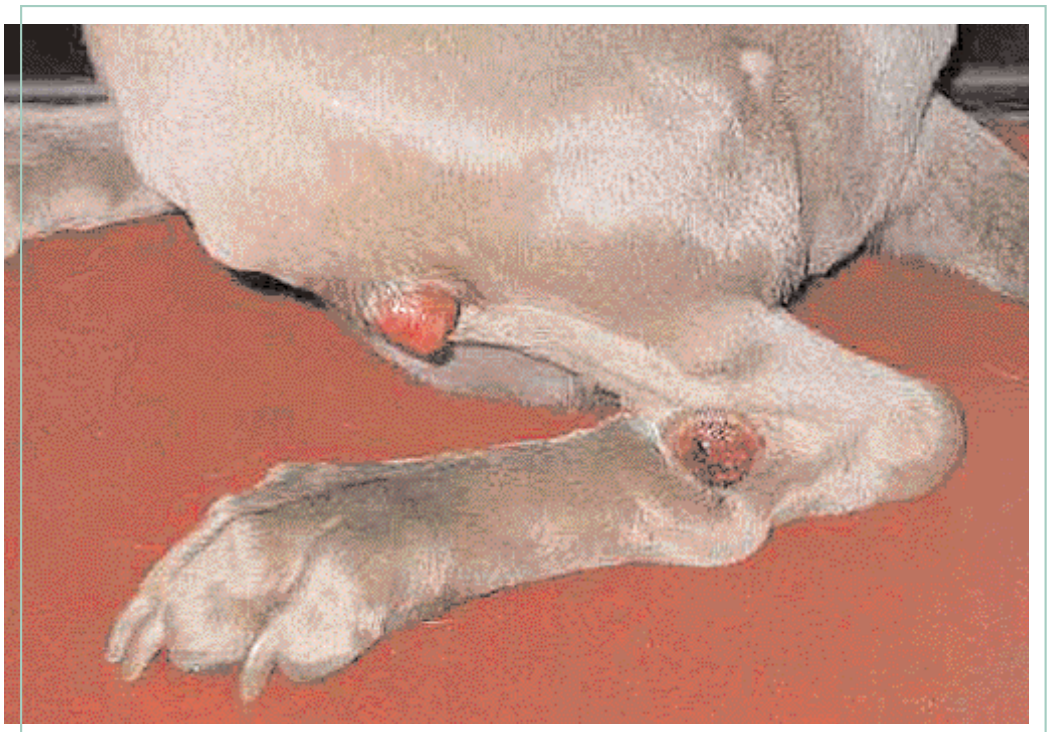

Figure 3 - Multiple MCTs on the skin of a dog. ***Courtesy of Dr Candace Sousa.***

Prognostication of canine mast cell tumours

The main prognostic indicator is histological grade. However, there is considerable variability and controversy in determining the prognosis of grade II MCTs and over 40% of MCTs are classed as grade II. Adverse results in the course of MCTs (relapses) are defined as either local re-occurrence at or near the surgical site or the development of metastases. Grade I mast cell tumours have a very low relapse rate and carry a good prognosis. Grade III tumours have a high relapse rate. Murphy et al, 2004 confirmed the poor prognosis for grade III tumours as found by earlier authors such as Patnaik et al ,1984. These recent authors studied 340 cutaneous mast cell tumours derived from 280 dogs. The one-year survival rates for the dogs with grade I-III MCTs "were significantly different (P = 0.0001), being 100 per cent, 92 per cent and 46 per cent, respectively. The median survival time for the dogs with poorly differentiated tumours was 278 days, significantly shorter than that for the dogs with either intermediately or well-differentiated tumours, which were both over 1300 days."

The prognostication of tumours morphologically described as grade II is more difficult. The first issue is "What is a grade II tumour?". There is considerable variation between pathologists in interpreting sections (Northrup et al, 2005). Some pathologists refer to high and low grade II MCTs but this is not based on standard reproducible criteria. Seguin et al, 2001 studied 60 completely excised grade II MCTs in 55 dogs over a median follow-up time of 540 days. "Three (5 per cent) mast cell tumours recurred locally; median time to local recurrence was 62 days. Six (11 per cent) dogs developed another mast cell tumour at a different cutaneous location; median time to a different location was 240 days. Three (5 per cent) dogs developed metastases; median time to metastasis was 158 days." Weisse et al, 2002 had reported less optimistic findings in their retrospective study of 31 dogs with completely excised, grade II cutaneous MCTs. "Distant tumour recurrence developed in 22 per cent of dogs, and local tumour recurrence developed in 11 per cent of dogs; however, the vast majority of these animals were incompletely staged initially."

To better determine which subset of grade II tumours are likely to more malignant, techniques using immunohistochemistry or special stains have been used. Chromosome nucleolar organizer regions stained with silver (AgNORs) can be counted. AgNOR counts, higher than 2.25 (estimated over 100 cells) are indicative of tumours that have a tendency to relapse locally or metastasise. Presently, in Australia, AgNOR counting must be done manually and is extremely time consuming. The evaluation of C-KIT mutations offers potential for prognosis determination. The KIT protein is a tyrosine kinase receptor that is a product of the c-kit proto-oncogene. Tyrosine kinase inhibitors are discussed under treatment. Kiupel et al, 2004 found that "normal mast cells and some neoplastic mast cells express KIT mainly on the cell membrane, 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. Well-differentiated tumours weakly expressing KIT and poorly differentiated tumours having a high expression of KIT Proliferate cell nuclear antigen (PCNA) is another marker related to relapse rate. Increased PCNA counts are related to both local regrowth and metastasis. To the best of the author's knowledge, C-KIT and PCNA testing are not yet commercially available in Australia.

The location of mast cell tumours has been related to prognosis. It is believed that MCTs in the inguinal or perineal region, on the limb extremities, on the muzzle and in association with mucocutaneous sites have a poorer prognosis. This may be related to the behaviour of the tumour per se and/or the difficulty in achieving complete surgical excision. Sfiligoi et al, 2005 studied 37 dogs with MCTs in the inguinal or perineal region and 87 dogs with MCTs in other cutaneous locations. They concluded "MCTs in the inguinal or perineal region do not have a worse prognosis in regard to disease-free interval or survival time than do dogs with MCTs in other cutaneous locations. Treatment recommendations for dogs with cutaneous MCTs should be based on confirmed predictors of biological behaviour, such as histologic grade and clinical stage." Cahalane et al, 2004 reported similar findings and conclusions.

It has been accepted, on first principals, that incomplete resection of a mast cell tumour leads to an increased rate of local or distant re-occurrence. A recent study by Michels et al, 2002 has caused controversy. These researchers studied 31 cases of different grades of MCT (only 2 dogs with grade III were included in the study) and compared those dogs with clean surgical margins to those with histologically demonstrated tumour cells at the wound margins". They (surprisingly!) concluded "differences in tumor-related death or frequency of relapse between the two groups were not significant". The authors did however report significantly more dogs in the non-tumour-free margin group relapsed by 12 and 24 months postoperatively compared to the tumour-free margin group. As a qualification, the authors also state that "the lack of statistical support for an association between prognosis and histopathological tumor-free versus non-tumour-free margins may be a result of small sample size". Only two of 11 dogs in the nontumour-free margin group relapsed in the surgical field. The authors postulate the reasons may include "immunological responses eliminating microscopic tumour, alteration in a subpopulation of tumour cells in the tumor, not sustaining growth (such as lack of key growth factor removed by one subpopulation of cells), tumor dormancy or the observed mast cells in the tumor margins being a component of the inflammatory response versus tumor". This study needs to be repeated with a larger sample and with a longer follow-up time but may explain the occasional anecdotal reports of incompletely removed MCTs or tumours removed with small margins failing to recur.

FELINE MAST CELL TUMOURS

Two forms of feline MCTs are seen: the more typical mastocytic type and the less common histiocytic type. Siamese cats are predisposed to both types, particularly the histiocytic type. The histiocytic type is more benign and has a predilection for younger cats (average 2.5 years old). Mastocytic cases occur in older cats (8 years plus) and are of variable malignancy. Multiple nodules in cats under 4 years of age may undergo spontaneous remission.

The histological grading system based on differentiation, as used in dogs, is not of prognostic value in cats. Limited data from Johnson et al 2002, suggests mitotic rate (> 1 per 10 high power fields) may be a prognostic factor.

Table II – Factors affecting the prognosis of canine MCTs

Prognostic indicator	Notes
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. Inguinal 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

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 (4-8 mg/kg SID or EOD) and, if required, chlorambucil (20mg/m^2 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-presenting 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 distinct disease (Noli et al, 2004).

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 completely removed grade II MCT without evidence of systemic spread is generally good, however a percentage will relapse locally or metastasize (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-II 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.

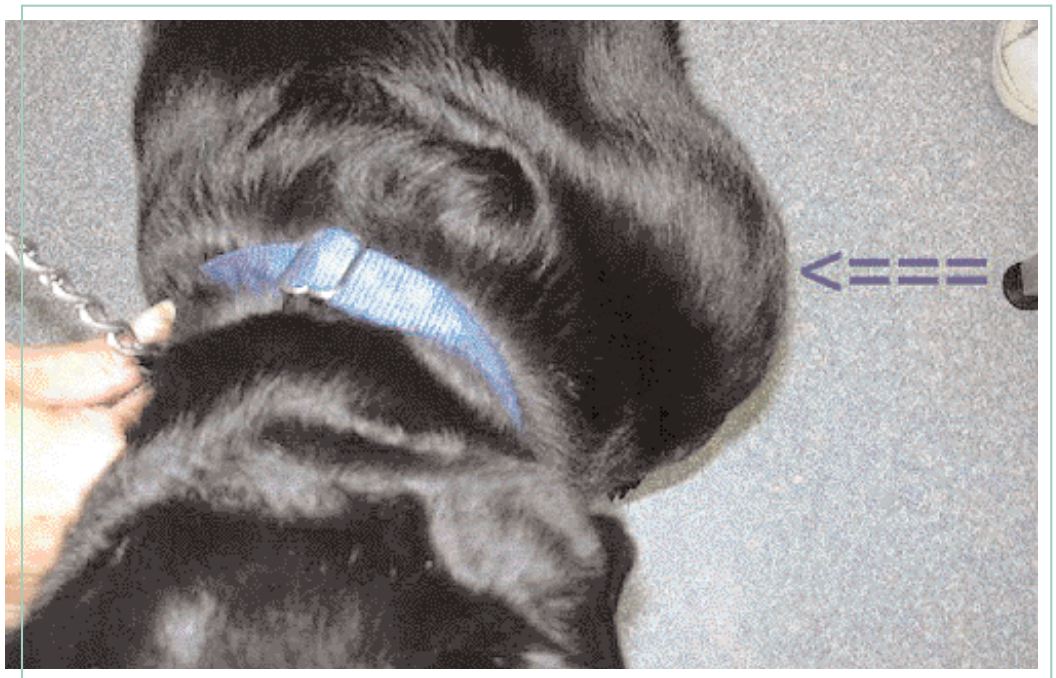

Figure 4 - Subcutaneous grade III MCT on the shoulder of a 7 year old Labrador. The mass had spread to the pre-scapular lymph node at the time of presentation. ***Courtesy of Dr Stefaan Van Poucke.***

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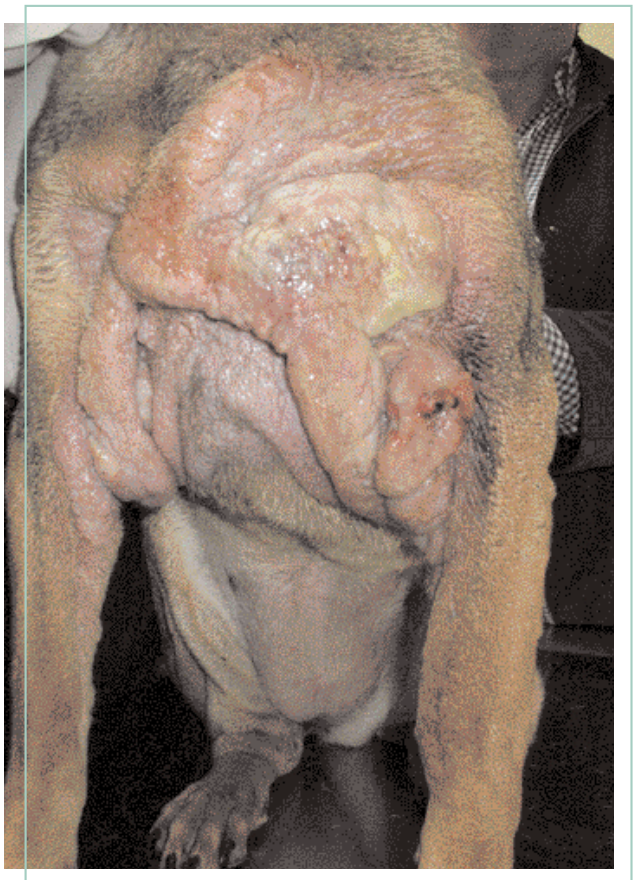

Figure 5 - Extensive grade III MCT with ulceration and inflammation on a 4 year old Shar Pei. ***Courtesy of Dr. Jacques Fontaine.***

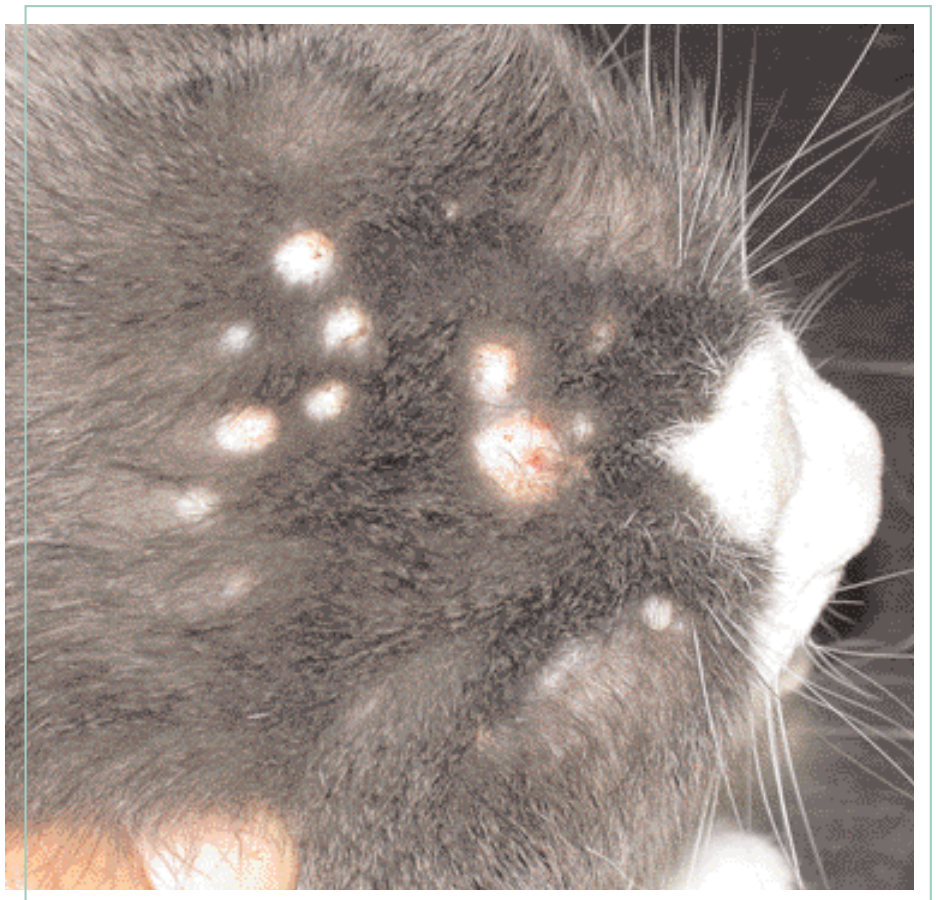

Figure 6 - Multiple MCTs on the head of a cat. In this case, the lesions were non-pruritic and no therapy was instituted. ***Courtesy of Dr Julie Delger.***

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