Cutaneous mast cell tumours in canines – diagnosis and staging

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Categories : Vets

Date : September 22, 2014

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in the first of a two-part article, discuss mastocytomas in dogs, breeds at risk, signs, diagnosis and staging

MAST cell tumours (MCTs) are reportedly the most common cutaneous tumour in the dog, representing up to 21 per cent of all canine skin tumours[1].

In addition to cutaneous sites, MCTs can occur as a primary or metastatic lesion at numerous other locations, including muscle[2], gastrointestinal tract, spleen and liver[3], larynx[4], spine[5], ureter[6], lymph nodes, bone marrow or in pleural/peritoneal effusions[1].

This article will discuss cutaneous MCTs. Several breed predispositions have been reported[7] – particularly the boxer (with an odds ratio – OR – of 6.09), Labrador retriever (OR 3.95), pug (OR 3.17), golden retriever (OR 2.12), and mastiff and terrier breeds[8].

Cutaneous MCTs are usually solitary, although it is not uncommon to see up to 10 per cent to 21 per cent of affected dogs (particularly at-risk breeds) develop multiple lesions noted either at initial

presentation or subsequently. These are generally considered to be multiple primary lesions, rather than metastases[9], but it is important to ensure they are not regrowth or a poorly differentiated tumour with satellite lesions[10].

In boxers and pugs, MCTs are usually of a low or intermediate histological grade (see later for grading information), carrying a more favourable prognosis. In Shar Peis, cutaneous MCTs are generally a higher histological grade and are biologically aggressive, carrying a more guarded prognosis[10].

History and signs

Affected animals may present for investigation of one or more mass lesions anywhere on the body, or the MCT could be identified incidentally during routine examination. Cutaneous MCTs are extremely variable in appearance (Figure 1), even in the same animal (Figure 2), and a significant minority of subcutaneous MCTs look and feel like lipomas[10]. Darier's sign is not uncommonly seen and is caused by the release of vasoactive amines from the mast cell granules, resulting in erythema and fluctuation of the mass size following trauma or manipulation[1] (Figure 3).

MCTs may develop rapidly over a period of several days or may have been present for several months/years without apparent change and, because the gross appearance correlates loosely with histological grade, the former is more likely to be aggressive and the latter is usually benign. However, a full investigation would always be preferable to relying on this assumption.

Additional clinical signs suggestive of aggressive behaviour include local irritation/ inflammation, local infiltration, ulceration, satellite nodules or paraneoplastic signs (for example, vomiting, anorexia, melaena and abdominal pain due to excessive histamine levels secondary to mast cell degranulation and stimulation of H_2 receptors on gastric parietal cells[11]; indeed, 35 per cent to 85 per cent of dogs with MCT had evidence of gastric ulceration at postmortem in one study, although all of the dogs had died as a result of mast cell tumour-related disease[12])[10].

Care must be taken when manipulating MCTs – particularly those suspected to be high-grade because a sudden massive release of histamine may cause an acute anaphylaxis and collapse[10]. Many clinicians anecdotally report delayed wound healing (due to proteolytic enzyme release) and local haemorrhage (due to local coagulation deficits caused by heparin) and the authors recognise this particularly with high-grade tumours. Interestingly, these findings have been disputed in a paper that showed incomplete mast cell tumour excision does not lead to a greater risk of wound complications compared with cutaneous histiocytoma wounds[13].

Diagnosis

Initial investigation of any mass should include cytological assessment of a fine needle aspirate (FNA) – samples from MCTs will demonstrate large numbers of cells from this readily exfoliative,

round cell tumour (Figure 4) and a diagnosis can be obtained by cytology alone in up to 96 per cent of cases[13,14].

A detailed description of the cells has been published[14] – MCT FNA will show large numbers of round cells containing intracellular granules. Nuclei are round to oval with aggregated chromatin; anaplastic cells may have binucleated cells and mitoses. The cytoplasm of the cells is filled with blue to purple granules (extracellular granules are also common). In low-grade tumours, the cells are readily cytologically identifiable as mast cells, but, in higher grades, the intracellular granules may be absent in anaplastic cells and, in such cases, immunocytochemistry can be helpful[1].

Histopathological grading

Histopathological grading of an MCT is the most important single prognostic factor. Most MCTs are diagnosed based on cytopathology alone; however, if preoperative biopsies are required, they should be performed in such a site that their excision may be readily included in the subsequent treatment protocols, without the need to enlarge the surgical site or radiation field.

The Patnaik system is the most widely used for cutaneous tumours[15] (Table 1), but is subjective, resulting in less than 64 per cent agreement between pathologists for grade one and two MCTs and 75 per cent agreement for grade three[16,17]. To reduce subjectivity, a two-tier system described by Kiupel has attempted to differentiate MCTs simply into high or low grade, resulting in a median survival time of less than four months and more than two years for high-grade and low-grade MCTs, respectively[17].

In Kiupel's grading system, a diagnosis of a high-grade MCT is based on the presence of any one of the following criteria: minimum of seven mitotic figures per 10 high-power fields (hpf); minimum of three multinucleated (three or more nuclei) cells per 10 hpf; minimum of three bizarre nuclei per 10 hpf; and/or karyomegaly (that is, nuclear diameters of at least 10 per cent of neoplastic cells vary by at least two-fold)[18].

Masses that do not fulfil this criteria are considered to be low-grade. A paper showed cytological assessment of MCTs correctly predicted the histological Kiupel grade, with an accuracy of 94 per cent, sensitivity of 84.6 per cent and specificity of 97.3 per cent; however, four per cent of high grade MCTs were not detected, which represents a limit to the overall utility of the technique[16].

Cell proliferation markers

Cell proliferation markers can also predict prognosis in response to therapy in a less subjective fashion. Mitotic index of greater than five and greater than seven is prognostic for reduced survival and increased recurrence, respectively[18,19].

Increased Ki-67, MCM7 and AgNOR scores are all associated with increased mortality, recurrence

and metastasis, independent of histological grade[20],[21],[22],[24]. Finally, increased proliferating cell nuclear antigen is associated with recurrent tumours and metastatic tumours, but is not independent of histological grade[21],[22],[23].

Mutations in the c-Kit gene are detected in 15 per cent to 40 per cent of canine MCTs and is associated with increased metastasis and local recurrence and highly histological grade[24],[25].

Staging

Once MCT has been cytologically confirmed, staging is recommended if an extensive or expensive treatment is planned or if a poorly differentiated tumour has been identified, and should include a minimum of FNA of draining lymph nodes and abdominal ultrasound[10]. Interpretation of lymph node FNA is challenging because up to 24 per cent of normal dogs have morphologically normal mast cells present in the sample[26], so it is generally agreed the mast cells must appear in clusters or sheets, rather than singularly, or must be grossly abnormal to call the sample “metastatic”.

Where nodal metastasis has been confirmed, abdominal ultrasound should be accompanied by an FNA of the spleen and liver. Thoracic imaging may also be required[10]. If chemotherapy is planned, complete blood count and serum biochemistry may be prudent if the animal may have concurrent illnesses or requires multiple anaesthetics (for example, for radiation therapy). It is worth noting buffy coat assessment in the dog has limited value because other clinical conditions (for example, vomiting and diarrhoea) can also cause an increase in circulating mast cell tumours in this species (but note buffy coat assessment is potentially still useful in cats)[27].

Owners should be warned subungual, scrotal and preputial mast cell tumours are associated with more aggressive biological behaviour compared with subcutaneous and cutaneous MCTs at other sites[1],[28]; however, this may also be due to the difficulty of achieving adequate surgical margins in these locations and studies are required to further elucidate this[10].

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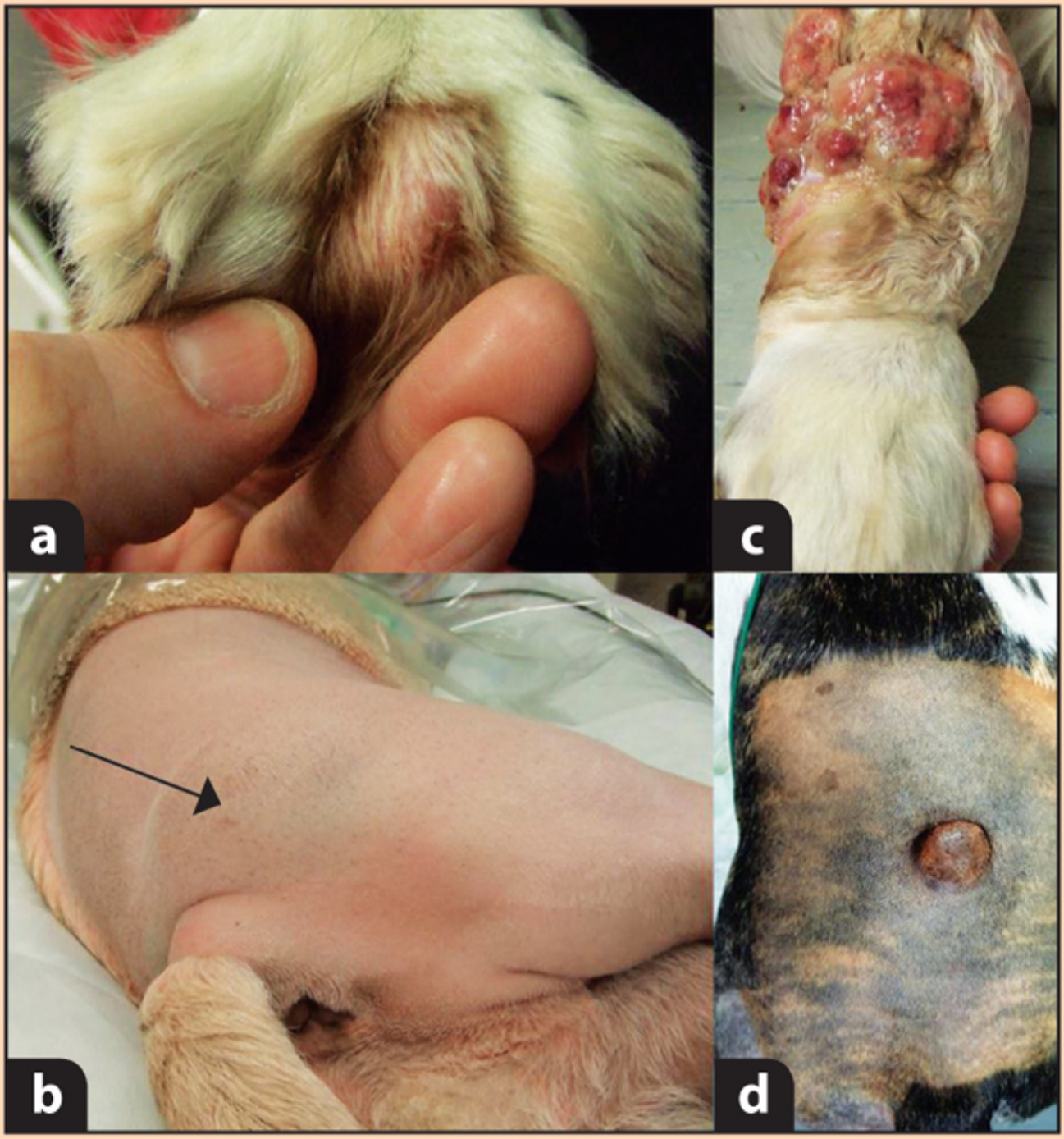

Figure 1. (a) Small interdigital cutaneous MCT that has been present for a week in an eight-year-

old crossbreed dog. (b) Poorly circumscribed cutaneous MCT over the right hip that has been present for a month in a five-year-old Labrador retriever. (c) Circumferential, ulcerative cutaneous MCT on the antebrachium of a 15-year-old springer spaniel that had been progressing for more than six months. (d) Well circumscribed cutaneous MCT on the dorsum of a five-year-old Staffordshire bull terrier that has been present without gross changes for several years.

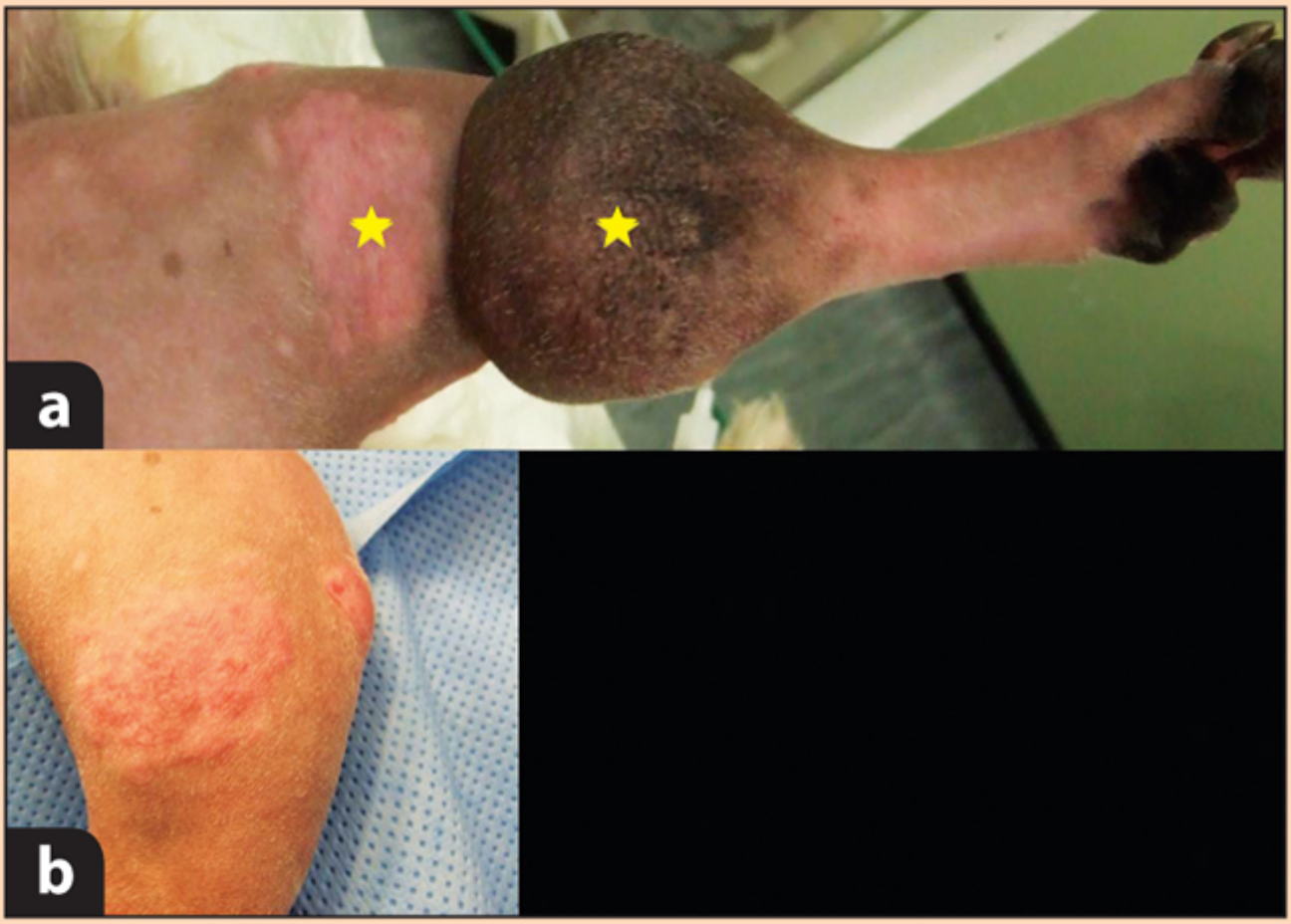

Figure 2. (a) Two high-grade mast cell tumours (I) on the right hindlimb of a three-year-old, neutered, male West Highland white terrier. The more proximal (left) mass is plaque like, has occurred rapidly and is seen close up in (b). The more distal mass (right) is soft and pendulous, and has developed over several weeks.

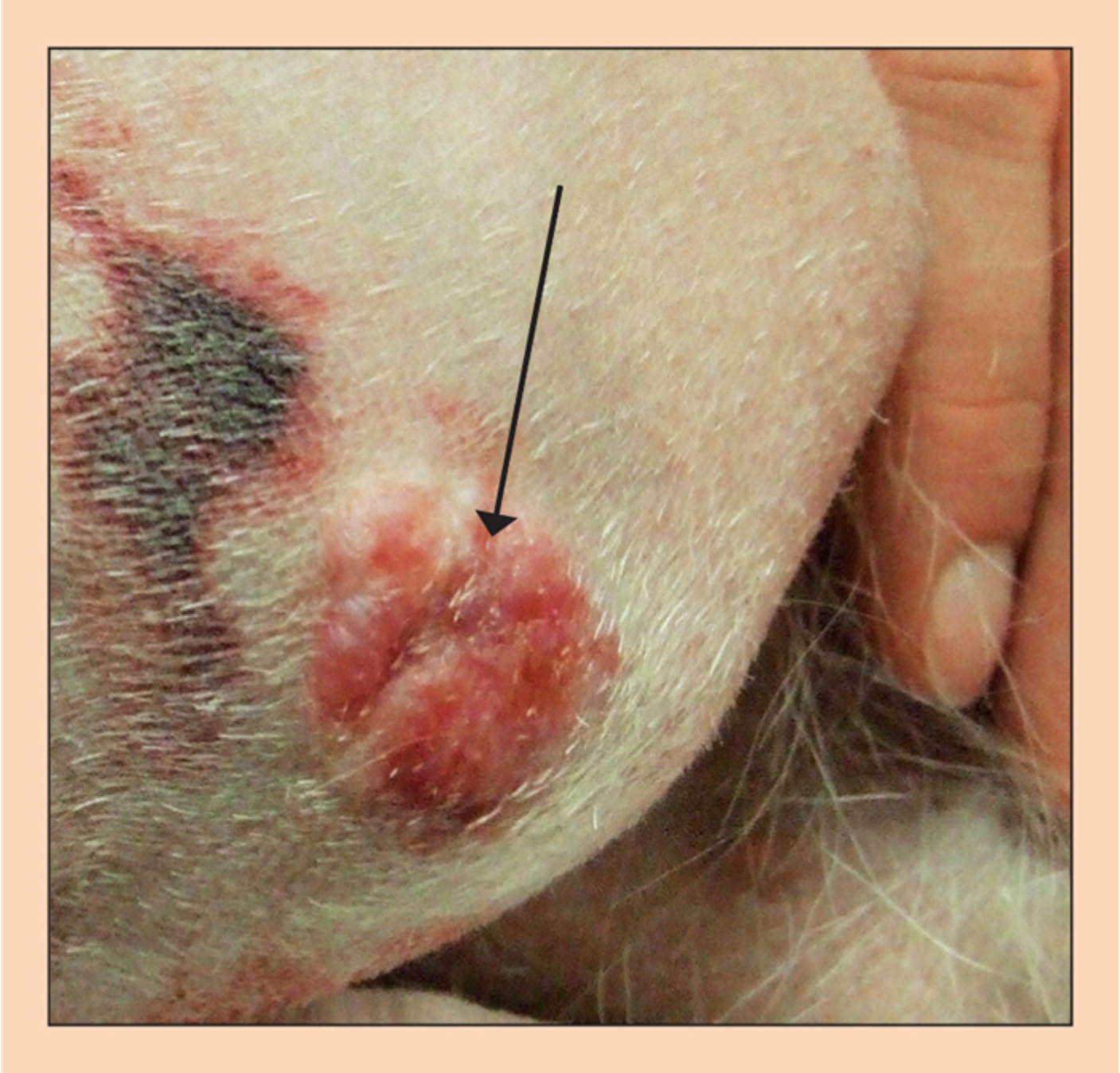

Figure 3. Darier’s sign associated with a small cutaneous mast cell tumour in a crossbreed dog following blunt trauma to the region.

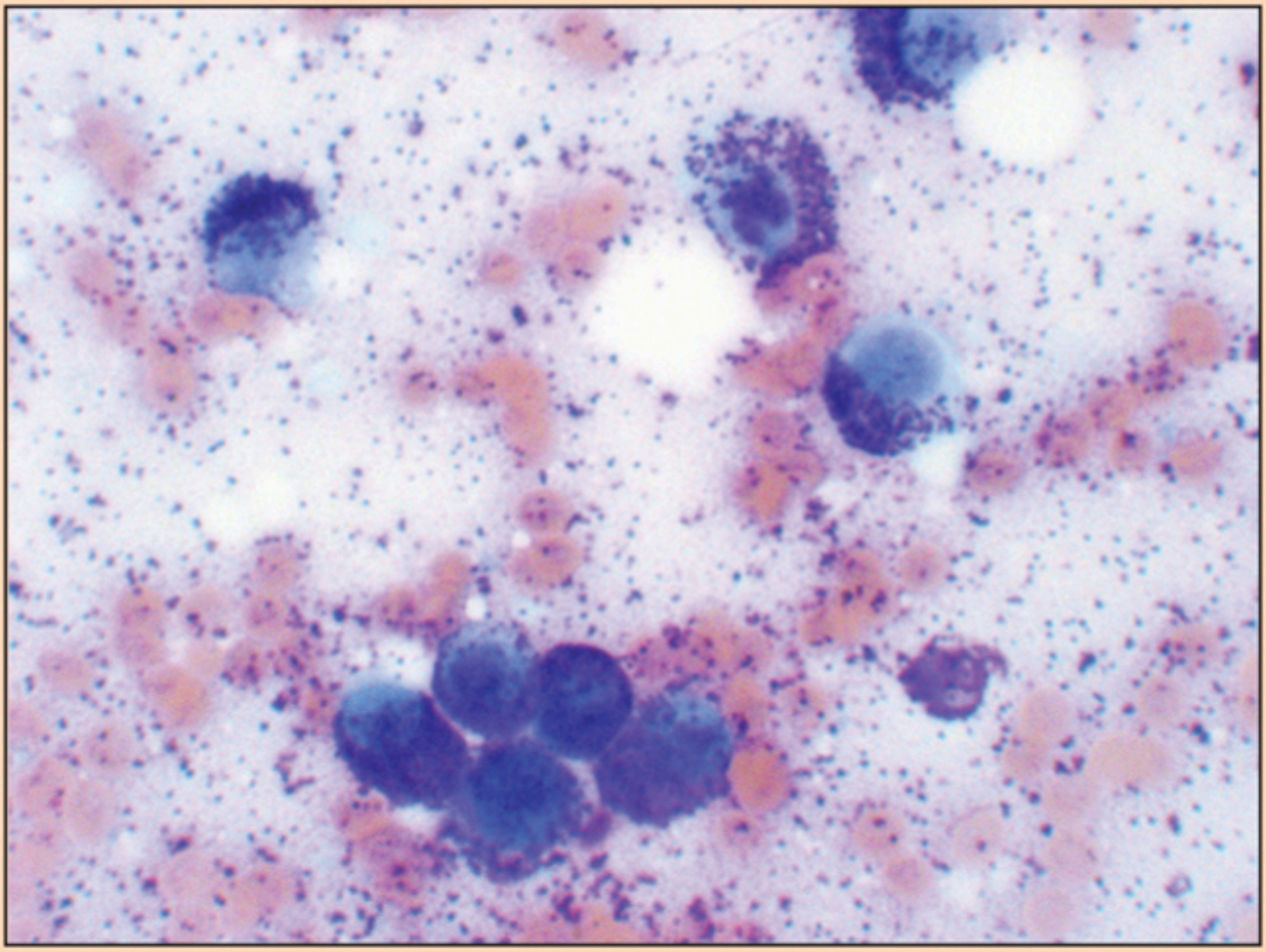

Figure 4. Cytological assessment of a fine needle aspirate from a MCT demonstrating large numbers of round cells containing intracellular granules. Nuclei are round to oval with aggregated chromatin; anaplastic cells may have binucleated cells and mitoses. The cytoplasm of the cells is filled with blue to purple granules and extracellular granules are also common (haematoxylin and eosin stain).

IMAGE: Jennifer Stewart.

Grade		Histological criteria	Clinical behaviour	Metastasis	Prognosis
1	Well differentiated	Monomorphic round cells with distinct cytoplasm, medium-sized intracytoplasmic granules, no mitotic figures, neoplastic cells confined to the dermis.	Develop slowly and may be static for years	< 10%	Excellent if local disease can be controlled. Unlikely to cause death.
2	Intermediately differentiated	More pleomorphic population, with some cells or ovoid in shape, distinct cytoplasm with fine intracytoplasmic granules, areas of oedema or necrosis, mitotic figures 0-2 per high-powered field, neoplastic cells infiltrating the lower dermis/subcutaneous tissue.	Variable	5-22%	May be cured by surgery. May cause death in 17-56% of patients due to local treatment failure or metastatic disease.
3	Poorly differentiated	Pleomorphic cells with indistinct cytoplasm with fine or absent intracytoplasmic granules, mitotic figures 3-6 per high-power field, oedema, haemorrhage, necrosis, ulceration, neoplastic cells infiltrating lower dermis/ subcutaneous tissue.	Aggressive rapid growth and high rate of recurrence	> 96%	Frequently the cause of death in affected patients.

Table 1. Histological criteria for Patnaik grading of mast cell tumours[10,15]