Cutaneous mast cell tumours – staging and histological grading

Author: MELANIE DOBROMYLSKYJ

Categories: Vets

Date: September 1, 2014

MELANIE DOBROMYLSKYJ BSc, Vet Path(Hons), BVSC, PhD, MRCVS considers the importance of histological grading of mast cell tumours as a screening tool and looks at both traditional and newer grading systems

Summary

The combination of the high incidence of cutaneous mast cell tumours in dogs, together with their highly variable and potentially fatal biological behaviour, and the potential for a plethora of paraneoplastic effects, means accurate prognostication and staging of mast cell tumours is vital. The single most valuable prognostic factor is still the histological grade of the tumour.

This article looks at the importance of case signalment, clinical staging and also the histological grading of these tumours, together with some of the problems with both the traditional Patnaik and Bostock grading systems and a more recently developed two-tier system. Despite the limitations, grading of mast cell tumours is still highly recommended as an initial screening tool at the time of routine histologic examination and diagnosis, also taking into account the staging of the disease, completeness of surgical margins and the location of the tumour.

Key words

mast cell tumour, prognostication, histological grading, staging
MAST cell tumours are common in dogs, making up between seven and 21 per cent of all cutaneous neoplasms in this species. This is a very high incidence, especially in comparison to humans where this tumour type is rare.

The biological behaviour of canine mast cell tumours can vary from benign solitary tumours, which are cured by complete surgical excision, to potentially fatal metastatic malignancies.

Furthermore, degranulation of mast cell tumours can result in paraneoplastic syndromes due to the release of histamine, heparin and other bioactive substances. These effects can be local to the tumour and include localised haemorrhage and/or oedema and wound dehiscence. Alternatively, these effects can be systemic, such as hypotension, haemorrhage, vomiting, gastrointestinal ulceration, anaphylactic shock and even death.

Affected dogs are typically middle aged (seven to nine years), but can range from as young as four weeks up to 18 years. There is no apparent sex predilection; however, breeds reported to be at increased risk in the literature include boxers, pugs, bull terriers, Boston terriers, Labrador retrievers, Staffordshire terriers, fox terriers, golden retrievers, Australian cattle dogs, beagles, cocker spaniels, schnauzers, Shar Pei, English bulldogs and Rhodesian ridgebacks.

Some breeds have a tendency to present at a younger age; the boxer is one breed that tends to develop low or intermediate grade tumours with a more favourable prognosis, while Shar-Pei frequently have more aggressive tumours.

Mast cell tumours can be single or multicentric, with between five per cent and 25 per cent of dogs affected with multiple skin tumours, either synchronously or sequentially. Several breeds have an apparent predisposition to multiple mast cell tumours, for example, golden retrievers, boxers, pugs, Weimaraners and Shar Pei. The skin is the most frequent location, but tumours can also occur in the intestine, liver, spleen, oral cavity and elsewhere. Tumours located in the oral cavity, mucocutaneous junctions, nail-bed, or inguinal, preputial or perineal regions are considered to behave in a more aggressive manner. Entirely subcutaneous masses generally carry a fairer prognosis.

Stage of disease is very important in terms of prognosis. The World Health Organization clinical staging system for mast cell tumours ranges from stages zero to four depending on the number of tumours, regional lymph node involvement and distant metastasis or recurrence. This system mirrors the expected path of metastatic spread of mast cell tumours, which tend to initially spread to local lymph nodes before metastasising to spleen, liver or other visceral organs. Lung involvement is very uncommon. Widespread systemic dissemination often results in the presence of neoplastic mast cells in peripheral blood and bone marrow.

Clinical stages zero and one carry the best prognosis. Although several studies have demonstrated stage two disease (disease involving a regional lymph node) can be successfully treated with
similar survival times to those seen with stages zero and one, other papers dispute this and find a decreased survival time with stage two disease. Some studies also criticise the definition of stage three disease, more specifically the “multiple dermal nodules” criterion, since their data suggest no difference in prognosis between animals with a single dermal tumour and those with multiple masses, and that each individual tumour should be staged separately. Some report dogs presenting with multiple mast cell tumours generally have a low rate of metastasis and good prognosis for long-term survival with adequate excision of all the masses.

A study in 2009 found cytological examination of fine needle biopsy aspirates from lymph nodes of dogs with mast cell tumours can provide useful information in terms of tumour staging and, thus, prognosis. This paper set out some useful criteria for examining lymph nodes in suspected cases of mast cell tumour metastasis, and correlated these criteria with both clinical outcome and mean survival times.

Categories for diagnosis start with normal or hyper-reactive nodes, through to possible, probable and certain metastasis, depending on the cell populations present and the number and size of clusters of mast cells seen (Figure 1). For possible metastasis, the mean survival time is 5.2 years, for probable metastasis it is 2.9 years, and for certain metastasis the mean survival time is 0.8 years. Thus, fine needle aspiration of regional lymph nodes, a non-invasive procedure, is an extremely useful component of the diagnostic investigation of mast cell tumour cases.

The combination of the high incidence of mast cell tumours, their highly variable and potentially fatal biological behaviour and the potential for paraneoplastic effects all mean that the accurate prognostication of mast cell tumours is vital. The single most valuable prognostic factor to date is the histological grade.

Two of the most commonly used histological grading systems for mast cell tumours are those reported by Bostock (1973) and Patnaik (1984). Both are three-tier systems, but unfortunately, they grade mast cell tumours in the opposite order to one another. Hence a well-differentiated mast cell tumour would be a grade I Patnaik, but a grade III Bostock, and a poorly-differentiated mast cell tumour would be a grade III Patnaik, but a grade I Bostock.

Also, both systems use slightly differing grading criteria; Bostock uses nuclear: cytoplasmic ratio, mitotic rate, tumour cellularity and the presence of granules, while Patnaik uses cell morphology, mitotic rate, tumour cellularity, tumour extent and stromal reaction (Table 2). Fortunately, most pathologists use the Patnaik grading system and also state whether the tumour is well-differentiated, of intermediate differentiation or poorly differentiated in addition to assigning a numerical grade, thus avoiding any confusion.

However, there are several problems with this system, one being a predominance of grade II (intermediate grade) tumours. Some of these grade II tumours are biologically aggressive, but are not distinguished as such because the Patnaik system has some grade III criteria that exclude...
these aggressive mast cell tumours from the higher category. Another problem is the criteria using any extension of neoplastic mast cells below the dermis and adnexa and into the subcutis; often this is the criterion that pushes an otherwise low-grade mast cell tumour towards being classified as a grade II rather than a grade I.

With both of these factors at play, it is little wonder grade II encompasses up to 59 per cent of all mast cell tumours, and this is a biologically diverse group of tumours (and ). This consequently means all grade II tumours have to be regarded as potentially malignant and makes it difficult to predict what additional therapy, if any, should be given to these dogs. Metastatic spread is reported to occur in five per cent to 22 per cent of grade II mast cell tumours, with local recurrence occurring in five per cent to 11 per cent; such a wide spread of figures between studies indicates just how biologically variable these grade II tumours can be.

In the original study by Patnaik, 43 per cent of mast cell tumours were given a grade II, and of those 56 per cent were dead due to the mast cell tumour at 1,500 days (five years). In other words, grading a mast cell tumour as a grade II really is of little prognostic value, since these dogs have about a 50:50 chance of dying due to their tumour in five years.

Pathologists are only too aware of the limitations of the grading schemes. The ability to distinguish the potentially malignant grade II minority from their relatively benign counterparts is something of a holy grail in diagnostic pathology. A new two-tier grading system was suggested, which avoids the use of tumour depth altogether. This system uses a mitotic count greater than seven mitotic figures per 10 high power fields (400×), together with karyomegaly (large nuclear size) and the presence of multinucleated cells (three or more) and/or bizarre nuclei.

Tumours are categorised as either low-grade or high-grade (Table 2). High-grade tumours were significantly associated with shorter time to metastasis or new tumour development and with shorter survival times. Median survival times were less than four months, but more than two years for high-grade and low-grade tumours respectively. However, this two-tier system was based on a relatively small study and the authors state it needs to be further validated in a prospective trial. As such, it has yet to be widely adopted by either pathologists or clinical oncologists.

Some groups have attempted to use mitotic index alone as a prognostic indicator, but this method still misses some of the biologically aggressive tumours. Cut-off values for distinguishing high-grade mast cell tumours vary between studies from five to 10 mitotic figures per 10 high power fields, which illustrates how unreliable mitotic index is as a sole prognostic indicator.

Grading systems for cutaneous mast cell tumours have not been validated for use in tumours arising elsewhere, including purely subcutaneous, oral and visceral masses. The subcutaneous variant of canine mast cell tumours is a distinct entity, which could be clinically confused with a lipoma. There is even a case report of a well-differentiated mast cell tumour arising in a lipoma in a boxer. These subcutaneous mast cell tumours often have histological features of an intermediate
grade (grade II) tumour, and such tumours are often graded as such by pathologists particularly due to their subcutaneous involvement (one of the criteria of grade II tumours). However, studies have shown these tumours often carry a slightly better prognosis than cutaneous mast cell tumours\textsuperscript{3, 4}, including relatively infrequent metastasis, low rates of recurrence and increased survival times. In this subcutaneous tumour variant, one study\textsuperscript{4} has shown decreased survival times are associated with multinucleation, an infiltrative growth pattern and an increased mitotic index, with a cut-off of greater than four mitotic figures per 10 high power fields. This study concludes such tumours should not automatically be graded as grade II due to their location in the subcutis.

Mast cell tumours arising in the oral cavity are far less common than their cutaneous counterparts and so less is known about their biological behaviour. However, two recent studies have looked at them as a separate entity. The first study\textsuperscript{1} looked at a number of mast cell tumours arising on the muzzle, but did not specify whether they were from haired skin or within the oral cavity. However, they concluded these tumours were biologically more aggressive and had an increased regional metastatic rate compared to those reported for mast cell tumours arising in other places. The second paper\textsuperscript{2} looked at tumours arising in the oral cavity, at the mucocutaneous junction and within the perioral skin, and also concluded that those arising in the oral cavity are more aggressive, with a high rate of lymph node metastasis, occurring in up to 59 per cent of cases.

Primary visceral mast cell tumours are also uncommon in dogs compared to cutaneous masses, and are much more common in cats than in dogs. Two studies have looked at these tumours\textsuperscript{16, 17} and found they typically arise in purebred miniature breeds. The Maltese terrier is especially over-represented, but these masses are also seen in other breeds, such as Chihuahuas and Yorkshire terriers. These studies concluded the prognosis in these cases was almost always poor, and pleomorphism of tumour cells did not appear to be related to the prognosis. Thus, grading systems such as Patnaik and Bostock are not useful in establishing a prognosis in primary visceral tumours.

Despite these limitations, grading of mast cell tumours is still highly recommended as an initial screening tool at the time of routine histologic examination and diagnosis of a cutaneous mast cell tumour, also taking into account the staging of the disease, case signalment, completeness of surgical margins and the location of the tumour.

References


Figure 1. Cytology sample from a regional lymph node. This sample was obtained from a fine needle aspirate biopsy of the right submandibular lymph node from a dog with an oral mast cell tumour, demonstrating a cluster of three mast cells (with purple-staining granules), with two further individual mast cells immediately adjacent. This would be categorised as a “possible metastasis”, using the criteria suggested by Krick et al (2009). Giemsa stain, 1000×, oil emersion.
Figure 2. A well-differentiated, Patnaik grade II cutaneous mast cell tumour. The figures illustrate the histological appearance of a well-differentiated Patnaik grade II (intermediate grade) canine cutaneous mast cell tumour. This mass involved the superficial subcutis, therefore would be categorised as a grade II. Note the mild to moderate variation in cell and nuclear size, the lack of mitotic figures, well-defined cytoplasmic granules and numbers of associated eosinophils. The mitotic rate in this tumour was two mitotic figures per 10 high power fields (400×). In the recently proposed two-tier system\textsuperscript{12} this tumour would be classified as low-grade. a) stained with routine H and E, (400x) b) stained with Giemsa, demonstrating large numbers of positive-staining granules in tumour cells (400x).
Figure 3. A less well-differentiated Patnaik grade II cutaneous mast cell tumour. The figures illustrate the histological appearance of a less well-differentiated Patnaik grade II (intermediate grade) canine cutaneous mast cell tumour. This mass more extensively involves the subcutis compared to the mass in Figure 2. Note the mitotic figure (arrow), poorly-defined cytoplasmic granules and increased variation in nuclear and cell size and shape. The mitotic rate in this tumour was 19 mitotic figures in 10 high power fields (400×). In the recently proposed two-tier system12 this tumour would be classified as high-grade. a) stained with routine H and E, (400×) b) stained with Giemsa, demonstrating variable numbers of positive-staining granules within tumour cells (400×)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>One tumour incompletely excised from the dermis identified by histological examination no lymph node involvement</td>
</tr>
<tr>
<td></td>
<td>a without systemic signs</td>
</tr>
<tr>
<td></td>
<td>b with systemic signs</td>
</tr>
<tr>
<td>1</td>
<td>One tumour confined to dermis without lymph node involvement</td>
</tr>
<tr>
<td></td>
<td>a without systemic signs</td>
</tr>
<tr>
<td></td>
<td>b with systemic signs</td>
</tr>
<tr>
<td>2</td>
<td>one tumour confined to dermis with regional lymph node involvement</td>
</tr>
<tr>
<td></td>
<td>a without systemic signs</td>
</tr>
<tr>
<td></td>
<td>b with systemic signs</td>
</tr>
<tr>
<td>3</td>
<td>multiple dermal nodules OR large infiltrating tumours with or without regional lymph node involvement</td>
</tr>
<tr>
<td></td>
<td>a without systemic signs</td>
</tr>
<tr>
<td></td>
<td>b with systemic signs</td>
</tr>
<tr>
<td>4</td>
<td>any tumour with distant metastasis OR recurrence with metastasis including blood or bone marrow involvement</td>
</tr>
</tbody>
</table>

**Table 1. The World Health Organization clinical staging system for mast cell tumours**
<table>
<thead>
<tr>
<th>MCT type</th>
<th>Patnaik grade: criteria</th>
<th>Bostock grade: criteria</th>
<th>Two-tier system: criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>I located in dermis low cellularity round, monomorphic cells distinct cell boundaries medium-sized granules round nucleus</td>
<td>III well-defined cell boundary regular, spherical nucleus N:C ratio &lt;0.55 MFs extremely rare</td>
<td>Low grade absence of any of the criteria below</td>
</tr>
<tr>
<td>Intermediate</td>
<td>II located in dermis and subcutis moderate to high cellularity round to ovoid, some pleomorphism scattered spindle and giant cells distinct cell boundaries fine granules round to indented nuclei occasional binucleated</td>
<td>II indistinct cell boundaries N:C ratio 0.55 - 0.7 cells more pleomorphic nuclei more often indented MFs infrequent cells closely packed</td>
<td>High grade any one of the following: a. at least 7 MFs in 10 hpfs b. at least 3 multinucleated cells (3+ nuclei) in 10 hpfs c. at least 3 bizarre nuclei in 10 hpfs d. karyomegaly</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>III infiltrates subcutis and deeper high cellularity round, ovoid, spindleloid pleomorphic cells indistinct cell boundaries fine granules or none indented or vesiculated nuclei with 1+ nucleoli multinucleated cells</td>
<td>I highly cellular, more closely packed indistinct cell boundaries irregular shaped nuclei N:C ratio &gt;0.7 MFs can be very frequent high degree cellular pleomorphism indented or vesiculated nuclei bizarre multinucleated giant cells</td>
<td></td>
</tr>
</tbody>
</table>

Grading systems summarised: Patnaik\(^5\), Bostock\(^5\) and the 2-Tier system\(^12\)

hpf – high power field (400x), N:C ratio – nuclear:cytoplasmic ratio, MF – mitotic figure
Table 2. Comparison of grading systems for canine cutaneous mast cell tumours