INTRODUCTION

Canine cutaneous mast cell tumors are one of the most common tumors in dogs, accounting for 7-21% of all canine cutaneous neoplasms. Although primarily occurring in older animals with an average age of 7.5 to 9 years, mast cell tumors have also been reported in animals younger than 1 year. These neoplasms are most commonly solitary, however, between 9 and 21% of affected animals will present with multiple masses. An increased incidence of cutaneous mast cell tumors has been reported in a variety of breeds: Boxers, Boston Terriers, Bull Mastiffs, Cocker Spaniels, Staffordshire Terriers, Fox Terriers, English Bulldogs, Dachshunds, Labrador Retrievers, Golden Retrievers, Beagles, Pugs, Schnauzers, Shar-Pei, Rhodesian Ridgebacks, Weimaraners and Australian Cattle Dogs. Multiple cutaneous mast cell tumors are reportedly more common in Boxers, Golden Retrievers, and Weimaraners. Boxers and Boston Terriers tend to develop more benign mast cell tumors while potentially aggressive varieties are found with greater frequency in the Shar-Pei and Labrador Retriever.

No consistent gender predilection has been associated with the development of mast cell tumors.

Mast cells do not mature in the bone marrow. Unlike other bone marrow derived cells, mast cell progenitor cells migrate to various tissues in the body and complete maturation at distant sites. Mast cells are most commonly found in tissues which interface with the environment. High numbers of mast cells are typically found in the
skin, gastrointestinal tract and lungs.

Mast cells have been historically identified by their prominent granules which stain strongly with cationic dyes. These granules contain a variety of mediators including: histamine, proteases, chemotactic factors, cysteine, and metabolites of arachidonic acid. Release of these mediators can be precipitated by immune mechanisms such as binding of immunoglobulins. Nonspecific stimuli including heat, trauma, and toxins may also precipitate granule release.

CLINICAL FACTORS AFFECTING PROGNOSIS

A major clinical dilemma associated with this relatively common skin tumor is that the biological behavior can vary from benign to a potentially fatal, metastatic disease. Early research focused on parameters that could be used as prognostic indicators. A variety of clinical factors were evaluated in an attempt to add prognostic information to the diagnosis of cutaneous mast cell tumors.

Although there are some contradictory reports in the literature, the site of the neoplasm does not appear to carry any significant prognostic values. Limb, head, trunk, inguinal region, scrotum, and tail prognostic value are related to the morphological features and mitotic rate of the neoplasm rather than location.

The gross appearance and growth rate of the neoplasm can give some prognostic information. Raised, well circumscribed, rubbery, cutaneous mast cell tumors tend to be lower grade and carry a better prognosis than poorly defined, edematous, ulcerated and erythematous tumors. More rapidly growing masses are often associated with a poorer prognosis. In general, the prognosis of an animal with multiple mast cell tumors is based upon the degree of atypia and mitotic rate seen in the least differentiated tumor, not the absolute number of tumors.

The World Health Organization clinically stages mast cell tumor neoplasia relating to the number of masses, lymph node involvement, and evidence of distant metastasis. Stages range from Stage 0 representing an incompletely excised mast cell tumor with no evidence of lymph node involvement, to Stage IV representing a tumor with distant metastasis and/or recurrence. In general, animals with Stage 0-I disease have a better prognosis than Stage III and IV. There have been reports of Stage II mast cell tumors (one dermal tumor with lymph node involvement) having a disease free interval similar to that of a Stage 0 animal after treatment.

Paraneoplastic syndromes secondary to release of mast cell granule constituents can be seen in approximately half of the dogs with mast cell tumors. Clinical signs can vary from delay in healing and prolonged bleeding at the surgical site to the potential of life threatening vomiting, hematochezia, anemia, and gastrointestinal perforation. Malignant mast cells contain 25-50 times more histamine than non-malignant mast cells. Gastrointestinal signs are typically associated with more aggressive mast cell tumor or extensive mast cell disease. While anaphylactic shock is not common, it can be seen in animals with extensive mast cell disease.

EARLY GRADING SYSTEM

The initial grading systems for mast cell tumors were introduced by Bostock in 1973 and Patnaik in 1984. Both of these grading schemes used a three tier system. Grade I was classified as low-grade in the Patnaik system but high grade in the Bostock system. Over the
decades, the Patnaik system became the more commonly used grading system by veterinary pathologists.

The Patnaik classification system grading criteria includes cellular morphology, mitotic index, cellularity, extent of tissue involvement, and stromal reaction to the neoplastic cells. Grade 1 tumors are composed of rows or clusters of well-differentiated mast cells retained within the dermis. No mitotic figures are identified. Grade 2 mast cell tumors are more cellular with some nuclear pleomorphism. These cells extend into the deep dermis, subcutis and occasionally deeper tissues with a rate of 0-2/10 high power fields (HPF). Grade 3 mast cell tumors are highly cellular with overtly pleomorphic cells, arranged in sheets which frequently efface normal dermal and subcutaneous architecture. There can be regions of hemorrhage and necrosis with mitotic rates of 3-6/10 HPF or greater. For decades this classification scheme was used as a general prognostic tool. The overwhelming majority (93%) of animals with Grade 1 mast cell tumors survived over 1,500 days. This is significantly better than the reported 47% of Grade 2 and 6% of Grade 3 affected animals.

Over the years, it became apparent that multiple factors and variables affected the classification system and thus patient prognosis. Many tumors expressed a variety of classification criteria that did not fit neatly into one grade. This discrepancy resulted in a wide variation in not only gradation among pathologists but also prognostic accuracy. Studies showed most mast cell tumors (approximately 50%) were classified as Grade 2 with significantly fewer Grade 1 and Grade 3 tumors. Forty-six percent of the patients with a Grade 2 tumor were alive at greater than 1,500 days in the Patnaik study. It became clear that little useful information had been given to clinicians by erroneously stating that the majority of cutaneous mast cell tumors had an approximately 50/50 chance of living past 1,500 days. Furthermore, additional studies found the majority of the Grade 2 mast cell tumors were cured by wide surgical excision; however, there still remained a percentage (5-22%) that would metastasize. These variables resulted in a general guarded prognosis for most mast cell tumors except for the most well differentiated and pleomorphic varieties.
TWO-TIER GRADING SYSTEM

One of the more recent efforts to improve mast cell tumor prognostication was to revisit the tumor grading system. One of these efforts was to limit the histopathological classification of mast cell tumors to two grades, low grade and high grade. This system, proposed by Kiupel in 2011, was created in an attempt to decrease the frequent overlap of classification between Patnaik Grade 1 and Grade 2 tumors and to increase veterinary pathologist consistency in classification. This two-grade system also improved prognostic accuracy. Grading criteria outlined in the Kiupel system include the mitotic rate and nuclear features including karyomegaly; multinucleated cells; and bizarre, uninucleate cells. The new high grade classification included identification of any one of the following criteria: a tumor with seven or greater mitotic figures per 10 HPF, three or greater multinucleated cells per 10 HPF, three or greater bizarre nuclei in 10 HPF, and karyomegaly characterized by 10% of cells exhibiting nuclei varying by at least twice normal size. The new classification system also came with new prognostic estimations. Low grade mast cell tumor patients survived for two years or more, while high grade mast cell tumor patients survived approximately four months.

The two tier grading system does not specifically address mast cell tumors which originate in and are confined to the subcutis. These are general guidelines of course, and the authors have clearly stated that morphological assessment of canine mast cell tumors has limitations as it relates to biological behavior.

PROLIFERATION MARKERS

Uncontrolled cellular proliferation is the basis of cancer. The study of cellular mechanisms relating to proliferation is offering new opportunities to further assess the likelihood of

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mast cell tumors exhibiting a more aggressive, biological behavior. Mitotic rate is a simple measure of cellular proliferation and does not require complicated staining techniques as do some of the new proliferation markers. From the early days of Bostock and Patnaik, the mitotic rate has been and remains an important tool to assess potential biological behavior of mast cell tumors.

One of the earlier tests employed to assess cellular proliferation is the identification of argyphilic nuclear organizing regions (AgNORs). These regions of the nucleus are associated with proteins involved in ribosomal RNA transcription and are widely used as a marker for tumor metabolic activity. The number of AgNORs in a nucleus has been found to be proportional to the cell proliferation time or doubling rate. A number of reports have associated increased AgNORs to increased mortality, local recurrence, and metastatic disease.

Ki67 is a nuclear protein expressed in all active cycling cells but absent in non-cycling cells. The number of positive cells in a tumor is used to calculate a proliferation index or relative percentage of cells in active cell growth. A high Ki67 expression is also associated with increased mortality, local recurrence, and metastatic disease. Ki67 may be a better indicator than AgNORs in detecting those tumors with a decreased survival prognosis. Ki67 has also been shown to be a prognostic indicator independent of the grade of mast cell tumor and can be used as an objective, prognostic marker, independent of histopathological tumor grade.

KIT is a cellular surface growth factor receptor encoded by the gene, c-KIT. Activation of KIT results in a cascade of chemical reactions promoting cellular proliferation, migration and maturation. KIT can be expressed in both normal and neoplastic mast cells. Mutations of the c-KIT gene are associated with increased expression of Ki67 and increased numbers of AgNORs. All neoplastic mast cells do not express mutation in the c-KIT gene, so it is likely other genes are also involved in mast cell disease progression. The presence of certain types of c-KIT mutations can be used to assess the likelihood of success using tyrosine inhibitor therapy for the treatment of mast cell tumors. Additional therapeutic research has investigated the use of anti-KIT receptor antibodies to block cell proliferation receptors on neoplastic mast cells.

CONCLUSION

The single, most important point to remember relating to prognosis of canine, cutaneous mast cell tumor disease is that no single factor accurately predicts the biological behavior. The etiopathogenesis of mast cell tumors is likely multifactorial and probably influenced by genetic factors. A mutation in cellular proliferation genes has been shown to play a key role in a significant number of mast cell tumors.

Diagnostic workup for mast cell tumors should include excision and histopathological assessment and grading. The animal should also be evaluated for the presence of metastatic disease as well as clinical signs suggesting paraneoplastic syndrome.

Diagnosis of mast cell neoplasia is simple compared to an accurate assessment of biological behavior. Mast cell tumor gradation remains somewhat subjective and has limited value in predicting biological behavior, especially with intermediate grade tumors. Grading systems serve as a good screening mechanism to decide if additional tests are required. More objective parameters such as mitotic rate and proliferation markers are more likely to be useful in prognostication of biological behavior. Additional work setting

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the “cut off” values for these markers is still required. A variety of mast cell proliferation markers can be ordered through Marshfield Labs.

REFERENCES


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