Review Article

Trends in Agriculutre Science (ISSN:2583-7850)

Vol.2, Issue 4, April, 2023, Page: 204-209

Mast Cell Tumors in Dogs: A Mini Review

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https://doi.org/10.5281/zenodo.7811600

Abstract

Mast cells (MCs) are well known for their neoplastic transformation in single and multiple cutaneous mast cell tumours (MCTs), as well as visceral and systemic mastocytosis. Dogs are particularly susceptible to cutaneous MCTs, incidence of which ranges from 20.9% and 22.4% of all canine skin tumors. Although the exact cause of canine MCTs is unclear, it is most likely complex. The pathogenesis, clinical presentation, diagnostic workup including cytological findings, immunohistochemistry, proliferation markers, special staining, histological findings, and grading system that have been assessed based on morphology are all reviewed in this article.

Introduction

Mast cell tumors (MCTs) are hematopoietic neoplasms characterized by uncontrolled proliferation and/or accumulation of neoplastic mast cells (MCs) in various organ systems (Meuten, 2020). The biological behaviour of canine mast cell tumors can vary from benign solitary tumours, which are cured by complete surgical excision, to potentially fatal metastatic malignancies. The incidence ranges from 20.9% and 22.4%, revealing MCT as the second-most frequent malignant neoplasm in dogs, after mammary gland tumors (McNiel *et al.*, 2006).

The skin is the most frequent location, but tumours can also occur in the intestine, liver, spleen via metastatic spread through regional lymph node. Cutaneous MCTs are most common on the trunk (50–60%), followed by the extremities (25– 40%), and the head and neck (10%). In general, a greater number of tumours affect the posterior part of the body (hind limbs, perineum and prepuce). Tumours

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Published: 09 April 2023

located in the oral cavity mucocutaneous junctions, nail-bed, or inguinal, preputial or perineal regions are considered to behave in a more aggressive manner (Welle *et al*, 2008). Mast cells have cytoplasmic granules and when stained with cationic dyes that bind granule proteoglycans, resulting in metachromasia.

Some breeds are predisposed to MCT development, including Boxer, Bull terrier, French bulldog, Labrador retriever, Dachshund, Golden retrievers, Beagles, Pugs, Schnauzers, Shar-peis, Rhodesian ridgebacks, Weimaraners and Australian cattle dogs. It is reported that in Boxers and boston terriers relative risk of MCT developement was 16.7 and 8.0 percent respectively may be related to their common bulldog ancestry (Welle *et al.*, 2008). Site predilection in Boxer and Pugs commonly found to be hind limbs and multiple lesions, in Boston terriers and American Staffordshire terriers hind limb, the tail in Rhodesian ridgebacks, multiple lesions in Weimaraners and Golden retrievers, and the head and hind limbs in English setters (Welle *et al.*, 2008). The Boxer is one breed that tends to develop low or intermediate grade tumours with a more favourable prognosis, while Shar-Pei frequently has more aggressive tumours (Giantin *et al.*, 2012). There is no known sex or age predilection, but the risk of developing cutaneous MCTs increases with age and the mean age of dogs developing MCTs is 9 years. However, it is also reported in dogs aged 4 to 6months (McNiel *et al.*, 2006). Mast cell tumours can be single or multicentric, with between 5 % to 25 % of dogs may get affected with multiple skin tumours which involves several breeds such as Golden retrievers, Boxers, Pugs, Weimaraners and Shar Pei (Giantin *et al.*, 2012).

Pathogenesis

The etiology of MCTs is unknown but, recent work has implicated the stem cell factor and receptor tyrosine kinase (KIT) in the etiology of canine MCTs. KIT is a surface growth factor receptor, normally expressed on MCs and encoded by the proto-oncogene c-kit. KIT consists of an extracellular ligand-binding domain, a transmembrane region and a cytoplasmic tail with ligand-dependent tyrosine kinase activity (London *et al.*, 1996). Activated KIT binds and phosphorylates intracellular substrate proteins, initiating a signaling cascade that culminates in a wide array of biologic activities including proliferation, migration, maturation, and survival of MCs. The ligand for KIT is stem cell factor, also known mast cell growth factor. Several authors have reported a variety of c-kit mutations in canine MCTs, particularly in exon 11, including different point mutations and tandem duplications in the juxta membrane coding region. Mutations of c-kit, characterized by

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internal tandem duplications, produce a constitutively activated KIT protein in the absence of ligands, that leads to extracellular signal-regulated kinase phosphorylation (Webster *et al.*, 2007).

Diagnosis

Diagnosis of MCT can be done by its gross appearance, histology, immunohistochemistry (KIT), cytology, proliferation makers like Argyrophilic nucleolar organizer regions (AgNOR) and special staining.

- **Gross appearance**

Mast cell tumours vary widely in appearance. The most common gross appearance is a small, raised, well circumscribed mass that may be hyperemic, alopecic, ulcerated or look like normal skin. They may also appear as a poorly-defined, soft, fluctuant lesion. The tumours may become quite large, up to 30 cm, or may occur as a diffuse, inflamed, dermal thickening (Sledge *et al.*, 2016).

- **Histology**

MCTs are cutaneous as well as subcutaneous, if the tumor is located in the epidermis or outer dermis it is classified as a cutaneous MCT and if it is below these anatomic locations, it is subcutaneous MCT. In some tumors the neoplastic cells form rows or ribbons. Some tumors will have a marked amount of edema and hemorrhage that cause the formation of distinct blue foci where the tumor is located. In others, eosinophils are so numerous that an MCT is suspected at first observation. Eosinophils are almost always found in canine MCTs and can sometimes be the predominant cell type. Collagen lysis, sclerosis, edema, necrosis, and secondary lymphocytic inflammation are often seen in MCTs. At higher magnifications the neoplastic mast cells are round to polygonal with round central to slightly eccentric nuclei. The cytoplasm is of moderate amount, pale pink and contains granules which stain light gray/blue with hematoxylin and eosin (H&E) or purple with metachromatic stains (Meuten, 2020).

Histologically, for grading of MCTs the Patnaik garding system (Table 1) is most commonly used wherein there is three tier grading system for grading of MCTs which grades them as well differentiated (grade I), intermediate (garde II), poorly differentiated (grade III) on basis of cell morphology, mitotic rate, tumour cellularity, tumour extent and stromal reaction (Patnaik *et al.*, 1984).

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Table 1. Patnaik grading system

Well-differentiated (Grade I)	**Intermediate (Grade II)**	**Poorly differentiated (Grade III)**
Located in dermis	Located in dermis and subcutis	Infiltrates subcutis and deeper
Low celluartiy mast cells are seprated by collagen fibers	Moderate to high cellularity	High cellularity
Round, monomorphic cells with Distintct cell boundries	Round to ovoid, some pleomorphism with Distinct cell boundries	Round, ovoid, spindleloid pleomorphic cells with Indistinct cell boundries
Round nucleus	Round to intended nuclei, occasionally binucleated.	Indented or vesiculated nuclei with 1+ nucleoli multinucleated cells
Medium-sized granules	Fine granules	Fine granules or none

- **Cytology**

Cytology of MCTs reveal a discrete round-cell population with moderate amounts of cytoplasm containing purplish red cytoplasmic granules and centrally or ecentric nucleus with fine/smooth chromatin. Other cells found are eosinophils and/or plump spindle cells, presumably fibroblasts. Granules can be stained with Wright's, Giemsa, Leishman, Romanowsky-type stains. The degree of granularity varies between tumors. Low grade tumors are typically well-granulated while higher grade tumors can be poorly or well-granulated Nuclear criteria of malignancy for MCTs are anisokaryosis, binucleation, large nuclei, nucleoli, mitotic figures (Meuten, 2020).

- **Proliferation markers**

Uncontrolled cellular proliferation is a hallmark of cancer and, as such, measures of cellular proliferation have been extensively used in an attempt to predict behaviour in neoplastic disease. In veterinary medicine, the most commonly used methods include staining for argyrophilic nucleolar organizer regions (AgNORs), immunohistochemistry for proliferating cell nuclear antigen (PCNA), Ki67 and KIT, all of which have been investigated in canine MCTs (Welle *et al.*, 2008). AgNORs are areas in the nucleus that are associated with proteins, such as nucleolin and nucleoplasmin substructures, involved in ribosomal RNA transcription. They are widely used as a marker of tumour kinetics and tumour metabolic activity. AgNORs bind silver molecules and can be visualized by light microscopy using a silverbased histochemical stain. The quantity of AgNORs per nucleus has been shown to be proportional to the rate of cell proliferation or cell doubling time in vitro and the rate of

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tumour growth in vivo. A number of studies have shown that higher AgNOR counts in MCTs are associated with increased mortality, local recurrence and metastasis (Webster *et al.*, 2007).

At present, KIT immunohistochemistry reactivity and its pattern of distribution have been used as diagnostic criteria for canine MCTs (Welle *et al.*, 2008). Normal and abnormal patterns of KIT expression have been described including a "surface-associated" or membranous pattern with an immunopositivity of the cell membrane, a cytoplasmic perinuclear pattern (pattern I) where KIT is detected in the cytoplasm of neoplastic MCs close to the nucleus, a focal to stippled cytoplasmic pattern (pattern II) and a diffuse pattern (pattern III) where MCs have diffused KIT expression throughout the cytoplasm (Hillman *et al.*, 2010). It is reported that there is significant association between the KIT staining pattern and the Patnaik grading system wherein grade I was found to be associated with KIT expression patterns I and II and staining pattern III was strongly associated with the G2 and G3 MCTs (Giantin *et al.*, 2012).

PCNA is a protein that interacts with DNA polymerases, it acts as an important factor for DNA replication and repair, excess PCNA expression is most commonly seen in the S-phase of the cell cycle while Ki67 is a nuclear protein that is expressed in all active phases of the cell cycle (Welle *et al.*, 2008). Hence higher expression of PCNA and Ki67 can be linked with aggressive behavior of MCTs and vice versa.

- **Special staining**

Toluidine blue (TB) staining for MCT is one of the cheapest and confirmatory diagnostic method. It is a special stain owing to its metachromatic property. It is used to highlight components, such as mast cells granules, mucins and cartilage. It stains the mast cell granules as bluish to purple color (Meuten, 2020).

Conclusion

Mast cell tumors (MCT) are hematopoietic neoplasms characterized by uncontrolled proliferation and/or accumulation of neoplastic MCs in various organ systems. Incidence ranges between 20.9% and 22.4% in dogs. The skin is the most frequent location, followed by intestine, liver, spleen, oral cavity and elsewhere. Most commonly affected breeds are boxers, bull terrier, french bulldog, pug and shar pie. Tandem duplication in c-kit at exon 11 results in production of activated KIT protein causing abnormal proliferation, maturation and migration of MCTs. MCTs are small, raised, solitary, rubbery well circumscribed mass surrounded by inflamed and oedematous tissue. Metastatic spread includes regional lymph node, spleen, liver and bone marrow. Histologically MCTs are round to polygonal arranged in rows and ribbons consisting central or slightly eccentric

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nuclei having fine chromatin. IHC marker like KIT can be used to diagnose as well as to grade the MCT according to its pattern of localization.

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