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Canine Mast Cell Tumor: Molecular Pathogenesis and Diagnostic Advancement

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Abstract

Mast cell tumor is the second-most frequent malignant neoplasm in dogs, after mammary gland tumors. Overall prevalence rate of mast cell tumor is up to 0.27% of the total dog population and representing up to 21% of all cutaneous tumors in dogs. Mast cells were first discovered by Paul Ehrlich in the year 1878. Mast cells are widely distributed in connective tissues throughout the body. Biological behaviour of tumors is highly unpredictable and majority were found as solitary nodules in the skin. Middle-aged to older dogs are highly susceptible however no sex predisposition has been revealed. Tumor varies in shape, size and consistency according to its anatomical site and nature of tumor. In most of the cases, activating c-KIT mutations and aberrant KIT expression are leading cause of mast cell tumors. Ultimately, transphosphorylation of the KIT receptors activates of abnormal proliferation of mast cells. Diagnosis of mast tumors involves cytology, histopathlogy, special staining, and immunohistochemistry.

Introduction

Canine mast cell tumors (MCTs) represent one of the most frequently encountered neoplasms in small animal oncology accounting for 7-25% of all skin tumors and 11-27% of the malignant skin neoplasms and remain a major diagnostic and therapeutic challenge due to their highly variable biological behaviour (Kiupel, 2016; de Nardi *et al*., 2022). Although many MCTs pursue an indolent clinical course, others display aggressive growth, local recurrence, and metastatic spread, often accompanied by severe paraneoplastic syndromes (London & Seguin, 2003). Advances in molecular biology and diagnostic pathology over the

past two decades have significantly improved our understanding of mast cell tumorigenesis, particularly the central role of KIT signaling abnormalities (London *et al*., 2009). This review focuses primarily on the molecular pathogenesis of canine MCTs and highlights contemporary diagnostic approaches that aid in accurate classification, prognostication, and clinical decision-making.

Biology of Mast Cells and Their Neoplastic Transformation:

Mast cells are long-lived, granulated immune cells derived from hematopoietic stem cell precursors (Vukman *et al*., 2017). Following migration from the bone marrow, immature mast cell progenitors undergo terminal differentiation within peripheral tissues under the influence of local cytokines and growth factors (Kitamura *et al*., 2007). In dogs, mast cells are widely distributed in loose connective tissues, particularly within the skin, gastrointestinal tract, respiratory system, and perivascular regions (Walker *et al*., 2012; Fede *et al*., 2023). Their physiological functions include participation in innate and adaptive immune responses, modulation of vascular permeability, angiogenesis, tissue remodeling, and wound healing (Krystel-Whittemore *et al*., 2016).

Neoplastic transformation of mast cells is thought to arise from dysregulated proliferation and survival signaling, leading to autonomous growth and resistance to apoptosis. Unlike normal mast cells, neoplastic mast cells often exhibit aberrant receptor expression, altered mediator release, and enhanced proliferative capacity, contributing to tumor progression and systemic clinical manifestations (da Silva *et al*., 2014).

Molecular Pathogenesis of Canine Mast Cell Tumors:

Role of KIT Receptor and Stem Cell Factor:

The most extensively studied molecular abnormality in canine MCTs involves dysregulation of the KIT receptor tyrosine kinase (CD117) (Miettinen & Lasota, 2005). KIT is encoded by the c-KIT proto-oncogene and functions as the receptor for stem cell factor (SCF), a critical regulator of mast cell development, differentiation, survival, and migration (Tsai *et al*., 2022). In normal mast cells, ligand binding induces receptor dimerization and controlled activation of downstream signalling pathways.

In neoplastic mast cells, activating mutations in the c-KIT gene result in constitutive, ligand-independent phosphorylation of the receptor. This leads to persistent activation of downstream pathways such as PI3K/AKT, MAPK, and JAK/STAT, which collectively promote uncontrolled proliferation, resistance to apoptosis, enhanced survival, and increased mediator release.

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KIT Mutations and Structural Alterations:

Activating mutations in c-KIT are detected in a significant subset of canine cutaneous MCTs, most commonly involving internal tandem duplications or point mutations within the juxtamembrane domain (exon 11), and less frequently in exons 8, 9, or 17 (Zemke *et al*., 2004; Webster *et al*., 2006). These mutations disrupt the inhibitory regulatory function of the juxtamembrane region, resulting in continuous kinase activation. Tumors harbouring c-KIT mutations are often associated with higher histological grade, aggressive biological behaviour, increased metastatic potential, and poorer prognosis (London *et al*., 2009).

Additional Molecular Alterations:

Beyond KIT signaling, other genetic and molecular changes contribute to mast cell tumorigenesis. Alterations in tumor suppressor genes such as TP53, dysregulation of cyclin-dependent kinase inhibitors (including CDKN1A and CDKN1B), and aberrant expression of hormone receptors have been reported (Vozdova *et al*., 2019). Chronic cutaneous inflammation, repeated antigenic stimulation, and environmental irritants may also create a pro-tumorigenic microenvironment that facilitates mast cell proliferation and malignant transformation.

Clinical And Pathobiological Consequences of Mast Cell Mediator Release:

Neoplastic mast cells retain the ability to synthesize and release biologically active mediators such as histamine, heparin, proteases, cytokines, leukotrienes, and prostaglandins (Ryan *et al*., 2013). Excessive or uncontrolled degranulation contributes to many of the clinical signs associated with MCTs, including localized erythema, edema, ulceration, and bruising, as well as systemic effects such as vomiting, diarrhea, gastric ulceration, hypotension, and delayed wound healing (Lamb *et al*., 2019).

Diagnostic Approaches to Canine Mast Cell Tumors:

Clinical Characteristics:

Well differentiated tumors are small, slow-growing, non-ulcerated, non-encapsulated having minimal alopecia. Whereas poorly differentiated neoplasms are large, rapidly-growing, ulcerated and may show oedema in adjacent tissues.

Cytology:

Fine-needle aspiration cytology is considered the first-line diagnostic tool for canine MCTs due to its simplicity, rapid turnaround time, and high diagnostic accuracy.

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Cytologically, mast cell tumors are characterized by round to polygonal cells containing variable numbers of metachromatic cytoplasmic granules. Poorly differentiated tumors may exhibit reduced granularity, nuclear pleomorphism, anisokaryosis, multinucleation, and increased mitotic activity, which can complicate cytologic interpretation.

Recent cytologic grading schemes (Figure 1) incorporate nuclear features, granularity, and mitotic activity to stratify tumors into low- and high-grade categories, providing valuable prognostic information even before histopathological evaluation.

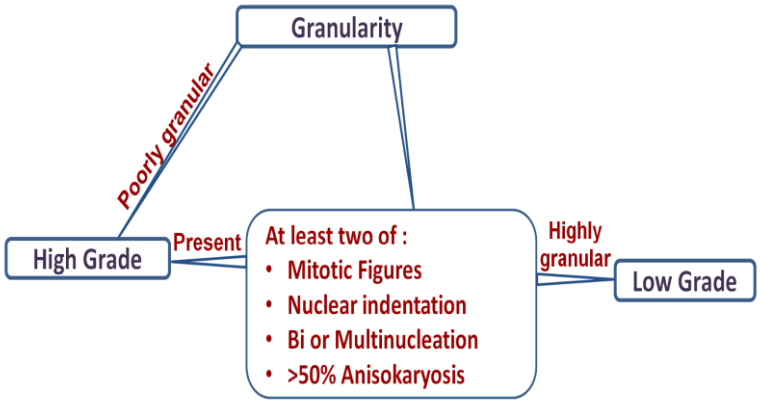

Figure 1: Cytologic grading scheme for MCTs

Histopathology:

Histopathological examination remains the gold standard for definitive diagnosis and grading of canine MCTs. Well-differentiated tumors are composed of relatively uniform mast cells with abundant granules, low mitotic indices, and minimal nuclear atypia. In contrast, high-grade tumors demonstrate marked pleomorphism, karyomegaly, increased mitotic figures, bizarre nuclei, and infiltrative growth patterns.

Among grading systems, the Kiupel two-tier histologic grading system (Figure 2) (Kiupel *et al*., 2011) is currently preferred over Patnaik three-tier system due to its improved reproducibility and prognostic relevance. This system classifies tumors as low-grade or high-grade based on defined mitotic counts, nuclear atypia, multinucleation, and karyomegaly.

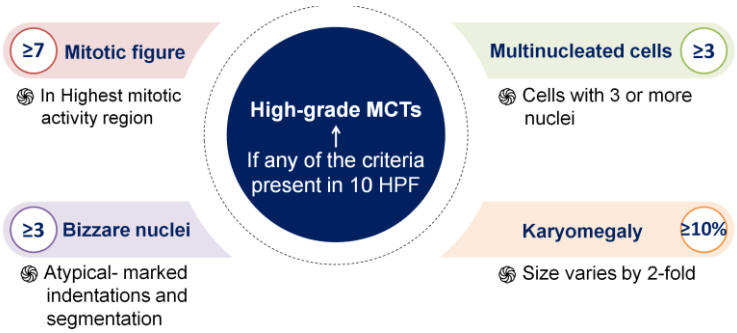

Figure 2: Kiupel 2- tier histologic grading system

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Special Staining Techniques:

Special histochemical stains such as toluidine blue and Giemsa are valuable adjuncts in cases where granules are poorly visualized on routine hematoxylin and eosin staining. Toluidine blue highlights mast cell granules through metachromatic staining, facilitating confirmation of mast cell origin, particularly in poorly differentiated tumors.

Immunohistochemistry and Molecular Diagnostics:

Immunohistochemistry (IHC) has emerged as a critical diagnostic and prognostic tool in canine MCTs. CD117 (KIT) immunolabeling confirms mast cell lineage and reveals distinct staining patterns that correlate with tumor behavior. Membranous KIT expression (Pattern I) is generally associated with well-differentiated, less aggressive tumors, whereas cytoplasmic or diffuse KIT staining patterns (Patterns II and III) are linked to c-KIT mutations and poorer prognosis.

Proliferation markers such as Ki-67 and AgNOR counts provide additional prognostic insight. Elevated Ki-67 indices and increased AgNOR numbers are strongly associated with aggressive behavior, higher metastatic risk, and reduced survival times.

Conclusions:

Canine mast cell tumors represent a biologically complex and heterogeneous group of neoplasms driven largely by molecular alterations in KIT signaling pathways. Advances in molecular pathology have clarified key mechanisms underlying mast cell tumorigenesis and have led to the integration of immunohistochemistry and proliferation markers into routine diagnostic workflows. A combined approach incorporating cytology, histopathology, special staining, and molecular diagnostics are essential for accurate classification and prognostication. Continued refinement of molecular diagnostic tools will further enhance individualized risk assessment and guide targeted therapeutic strategies in canine mast cell tumors.

REFERENCES:

da Silva, E. Z., Jamur, M. C., & Oliver, C. (2014). Mast cell function: a new vision of an old cell. *The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society*, *62*(10), 698–738. https://doi.org/10.1369/0022155414545334

de Nardi, A. B., Horta, R. S., Fonseca-Alves, C. E., & Amorim, R. L. (2022). Diagnosis, prognosis and treatment of canine cutaneous mast cell tumors: A review. *Veterinary and Comparative Oncology, 20*(2), 235–250.

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Published 28/12/2025

Fede, C., Petrelli, L., Pirri, C., Tiengo, C., De Caro, R., & Stecco, C. (2023). Detection of Mast Cells in Human Superficial Fascia. *International journal of molecular sciences*, *24*(14), 11599. https://doi.org/10.3390/ijms241411599

Kitamura, Y., Oboki, K., & Ito, A. (2007). Development of mast cells. *Proceedings of the Japan Academy. Series B, Physical and biological sciences*, *83*(6), 164–174. https://doi.org/10.2183/pjab.83.164

Kiupel, M. (2016). Mast cell tumors. In D. J. Meuten (Ed.), *Tumors in domestic animals* (5th ed., pp. 176–202). Wiley Blackwell.

Kiupel, M., Webster, J. D., Bailey, K. L., Best, S., DeLay, J., Detrisac, C. J., Fitzgerald, S. D., Gamble, D., Ginn, P. E., Goldschmidt, M. H., Hendrick, M. J., Howerth, E. W., Janovitz, E. B., Langohr, I., Lenz, S. D., Lipscomb, T. P., Miller, M. A., Misdorp, W., Moroff, S., Mullaney, T. P., … Miller, R. (2011). Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Veterinary pathology*, *48*(1), 147–155. https://doi.org/10.1177/0300985810386469

Krystel-Whittemore, M., Dileepan, K. N., & Wood, J. G. (2016). Mast Cell: A Multi-Functional Master Cell. *Frontiers in immunology*, *6*, 620. https://doi.org/10.3389/fimmu.2015.00620

Lamb, C. R., Whitlock, J., & Foster-Yeow, A. T. L. (2019). Prevalence of pulmonary nodules in dogs with malignant neoplasia as determined by CT. *Veterinary radiology & ultrasound : the official journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association*, *60*(3), 300–305. https://doi.org/10.1111/vru.12723

London, C. A., & Seguin, B. (2003). Mast cell tumors in the dog. *The Veterinary clinics of North America. Small animal practice*, *33*(3), 473–489. https://doi.org/10.1016/s0195-5616(03)00003-2

London, C. A., Malpas, P. B., Wood-Follis, S. L., Boucher, J. F., Rusk, A. W., Rosenberg, M. P., Henry, C. J., Mitchener, K. L., Klein, M. K., Hintermeister, J. G., Bergman, P. J., Couto, G. C., Mauldin, G. N., & Michels, G. M. (2009). Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *15*(11), 3856–3865. https://doi.org/10.1158/1078-0432.CCR-08-1860

Miettinen, M., & Lasota, J. (2005). KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation. *Applied immunohistochemistry & molecular morphology, 13*(3), 205–220. https://doi.org/10.1097/01.pai.0000173054.83414.22

Ryan, R. J., Akin, C., Castells, M., Wills, M., Selig, M. K., Nielsen, G. P., Ferry, J. A., & Hornick, J. L. (2013). Mast cell sarcoma: a rare and potentially under-recognized diagnostic entity with specific therapeutic implications. *Modern pathology : an official*

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journal of the United States and Canadian Academy of Pathology, Inc, *26*(4), 533–543. https://doi.org/10.1038/modpathol.2012.199

Tsai, M., Valent, P., & Galli, S. J. (2022). KIT as a master regulator of the mast cell lineage. *The Journal of allergy and clinical immunology*, *149*(6), 1845–1854. https://doi.org/10.1016/j.jaci.2022.04.012

Vozdova, M., Kubickova, S., Fictum, P., Fröhlich, J., Jelinek, F., & Rubes, J. (2019). Prevalence and prognostic value of c-kit and TP53 mutations in canine mast cell tumours. *Veterinary journal*, *247*, 71–74. https://doi.org/10.1016/j.tvjl.2019.03.005

Vukman, K. V., Försönits, A., Oszvald, Á., Tóth, E. Á., & Buzás, E. I. (2017). Mast cell secretome: Soluble and vesicular components. *Seminars in cell & developmental biology*, *67*, 65–73. https://doi.org/10.1016/j.semcdb.2017.02.002

Walker, M. E., Hatfield, J. K., & Brown, M. A. (2012). New insights into the role of mast cells in autoimmunity: evidence for a common mechanism of action?. *Biochimica et biophysica acta*, *1822*(1), 57–65. https://doi.org/10.1016/j.bbadis.2011.02.009

Webster, J. D., Yuzbasiyan-Gurkan, V., Kaneene, J. B., Miller, R., Resau, J. H., & Kiupel, M. (2006). The role of c-KIT in tumorigenesis: evaluation in canine cutaneous mast cell tumors. *Neoplasia*, *8*(2), 104–111. https://doi.org/10.1593/neo.05622

Zemke, D., Yamini, B., & Yuzbasiyan-Gurkan, V. (2002). Mutations in the juxtamembrane domain of c-KIT are associated with higher grade mast cell tumors in dogs. *Veterinary pathology*, *39*(5), 529–535. https://doi.org/10.1354/vp.39-5-529