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Imatinib in the Management of Canine Cutaneous Mast Cell Tumours

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ABSTRACT

Mast cell tumours are one of the commonly recorded cutaneous tumours in dogs which are seen as either solitary lesion or diffused ones. The present case study discusses about the use of tyrosine kinase inhibitor i.e., Imatinib mesylate in the management of cutaneous mast cell tumours in seven dogs presented to Madras Veterinary Teaching Hospital with cutaneous ulcerations, nodular lesions and exudation. Fine needle aspiration cytology and tissue biopsy were done to confirm the diagnosis of cutaneous mast cell tumours. All the case were treated with tyrosine kinase inhibitor i.e., Tab.Imatinib @10 mg/kg orally SID for 10 weeks along with Tab. Prednisolone @1 mg/kg SID orally for three weeks followed by tapering of the dose to 0.5 mg/kg in fourth week. Chlorpheniramine maleate @3 mg/kg SID and famotidine @ 0.5 mg/kg BID were also added to the protocol. Out of seven cases treated, four showed significant improvement by 5th week while two showed partial remission and one did not respond. Thrombocytopaenia, Anaemia and ulcerative gastritis were the complications seen during the therapy.

HIGH LIGHTS

- Study on tyrosine kinase inhibitor Imatinib in treatment of canine cutaneous mast cell tumours
- Imatinib was found to have good success in treating mast cell tumours with minimal side effects.

Keywords: Cutaneous mast cell tumour, Dogs, Chemotherapy, Tyrosine kinase inhibitor, Imatinib mesylate

Mast cell tumours (MCT) are one of the common cutaneous tumours in dogs (Shoop *et al*., 2015) constituting 20 per cent of the diagnosed cases (Kiupel and Camus, 2019). Mast cells are discrete round cells derived from bone marrow that reach various locations with access to foreign antigen like skin, gastrointestinal, pulmonary system etc., These cells release histamine, heparin, proteolytic enzymes etc., in response to foreign stimulus to exert a toxic effect over them (Dasa *et al*., 2014). Although mast cell tumour can affect visceral organs like liver, spleen etc., cutaneous form is the most common form. This cutaneous form in turn can result in metastasis to visceral organs (Bowlt Blacklock *et al*., 2018). Canine cutaneous mast cell tumours (MCTs) can occur either as solitary nodules or diffuse lesion that may be either cutaneous or subcutaneous. On appearance these are great pretenders with varying shapes like warts, lump or even ulcerated skin mass. Degranulation of the tumour cells results in huge volume of histamines that can cause a potential gastroduodenal ulceration. Diagnostically fine needle aspiration cytology is the most commonly employed test for MCT's and are cytologically characterized by predominant individualised monomorphic round cells with central to eccentric round nucleus and metachromatic granules (Kiupel and Camus, 2019). FNAC is useful to diagnose MCT however to differentiate cutaneous form from subcutaneous form,

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biopsy is the preferred technique. Several chemotherapies were reported to treat MCT's with varying complications and success. The present case study discusses about the novel targeted approach in treating cutaneous mast cell tumours using tyrosine kinase inhibitor drug i.e., Imatinib.

MATERIALS AND METHODS

A total of seven cases were presented to Madras Veterinary College Teaching hospital with the symptoms of cutaneous ulcerations, nodular lesions and exudation that are non-responsive to antibiotic therapy as well as topical medication were taken for the study (Fig. 1).

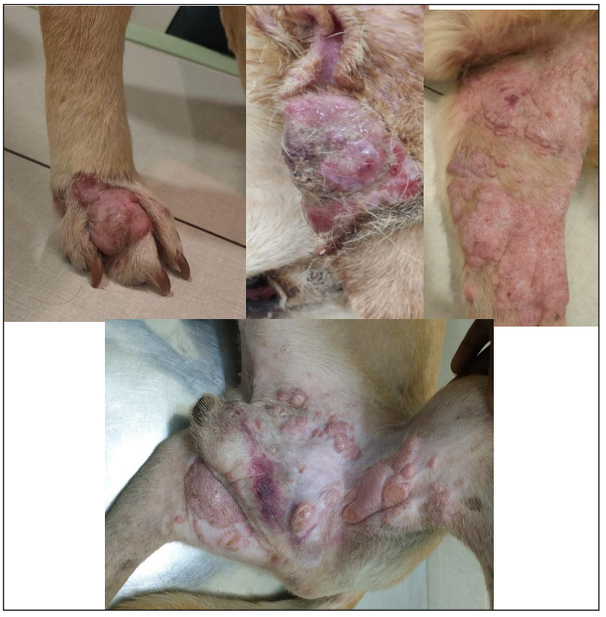

Fig. 1: Mast Cell Tumour – Pre therapy

All the cases were subjected to detailed dermatological examination and samples were collected for cytological examination. Complete blood picture and serum biochemical evaluation were also performed. All the cases were cytologically diagnosed as Mast Cell tumours (MCT's) (Fig. 2) which were also confirmed on histopathology (Fig. 3). No significant change was noticed in the haematological and biochemical evaluation. In all the seven cases treatment was initiated with tyrosine kinase inhibitor i.e., Imatinib @10 mg/kg orally SID for 10 weeks along with Tab. Prednisolone @1 mg/kg SID orally for three weeks followed by tapering of the dose to 0.5 mg/kg in fourth week. Chlorpheniramine maleate @3 mg/kg SID and famotidine @ 0.5 mg/kg BID were also added to the protocol. Chlorpheniramine was included in the protocol to counteract the chronic inflammatory signs of histamine that is in circulation as well as released further due to degranulation of the mast cell. Famotidine a H2 blocker protects the gastric mucosa from the life-threatening ulcerations that happen due to histamine. The outcome of the therapy is further discussed.

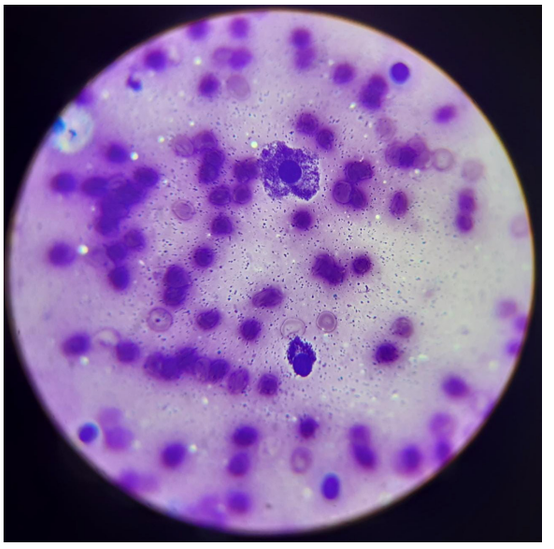

Fig. 2: FNAC showingpleomorphic mast cells containing basophilic granules Leishman stain X1000

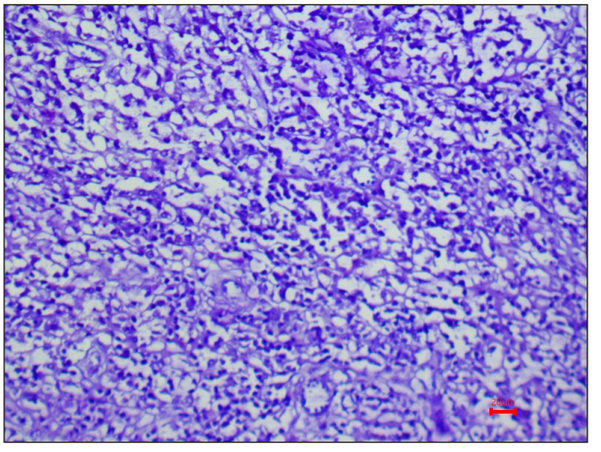

Fig. 3: Presence of metachromatic granules in cytoplasm of mast cell Toluidine blue Scale bar TB-100 µm

RESULTS AND DISCUSSION

Out of the seven cases, four cases showed significant improvement by 5th week after initiation of therapy with complete remission noticed by 10 weeks. Two cases showed partial remission while one case has not responded to the therapy (Fig. 4). Clinical side effects recorded were thrombocytopaenia in 3 cases and mild anaemia in 2 cases. Severe anaemia due to acute ulcerative gastritis is seen in one case as a result of withdrawal of famotidine by the owner. This case was treated with sucralfate @ 5 ml TID PO, Inj.Chlorpheniramine @ 0.3 mg/kg IM and Inj. Ranitidine @ 2 mg/kg IM. Blood transfusion done twice to restore the blood loss and was recovered by 5th day.

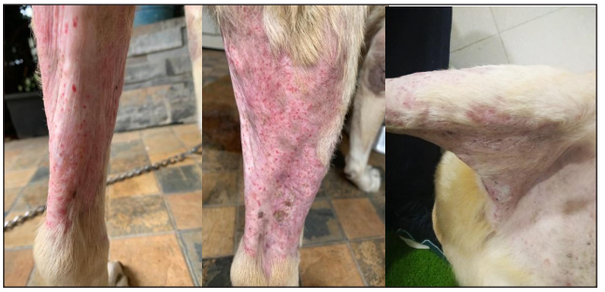

Fig. 4: Reduced exudation with healing of the lesions (5th day post treatment)

Till date various therapeutic options are available for mast cell tumours with surgical resection being the treatment of choice. In cases with site inaccessible for surgical resection, other therapeutic options are employed alone or in combination that include chemotherapy, hypotonic solution treatment, external beam radiation treatment, hypo fractionated radiation therapy, Interstitial brachytherapy etc., (Carlsten *et al.,* 2012). Chemotherapy being the most commonly practiced among the modalities with therapeutic agents having varied success depending on the stage of tumour. Single agent therapy with CCNU (lomustin, nitrosurea), prednisolone, multiagent therapy with VCHP (Vincristicine, cyclophosphamide, hydroxyurea and prednisolone) are studied of which the later showed good response rates (Blackwood *et al*., 2012). Other chemotherapeutic trials using chlorambucil and prednisolone was also done by some authors with measurable response. In canine mast cell tumour, KIT mutation is found to be important mechanism in the process of neoplastic transformation in mast cells. Signalling through the KIT receptor tyrosine kinase is crucial for cellular proliferation and survival. (Halsey *et al.,* 2017). With the advent of cKIT mutations and their role in pathogenesis of MCT, tyrosine kinase inhibitors are taken as the new line of therapeutic modality with low risk and high efficacy.

Imatinib is a tyrosine kinase inhibitor that acts on the c-KIT pathway and was found to be favourable in the treatment of canine MCT's (Kim *et al*., 2016). Imatinib has targeted effect on tyrosine kinases especially BCR-ABL, c-KIT, andplatelet derived growth factor receptor tyrosine kinase (PDGFRA) (Bonkobara, 2015). Though theoretically Imatinib can be used in MCT's with c-KIT mutation, certain reports indicated that they can successfully be used in treating cases without a cKIT mutation (Nakano *et al*., 2013) thus making it a suitable therapeutic agent in canine mast cell tumour. In the present study Imatinib was used in all the seven cases without evaluating c-KIT mutation however significant recovery was noticed in six out of the seven cases which revealed that Imatinib can safely be used in treatment of MCT irrespective of C-KIT mutation.

CONCLUSION

Effective chemotherapy with minimal or no side effects as well as no recurrence is the need of the hour for several tumours seen in Veterinary practice. Owing to the better tolerability and clinically fewer side effects, Imatinib can widely be used for the management of canine mast cell tumours.

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