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Treatment of a feline cutaneous mast cell tumour using imatinib mesylate as a neoadjuvant tyrosine kinase inhibitor therapeutic agent

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Abstract: A two-year-old spayed female American shorthair cat presented with a rough, circular, exophytic mass on the genital area. The clinical findings and histopathological examination revealed that the mass contained neoplastic mast cells and, thus, was diagnosed as a mast cell tumour. The anatomical location of the mass was not easily accessible for surgical intervention. We administered a targeted therapy using oral imatinib mesylate for eight weeks to reduce the size of the lesion and to facilitate the successful surgical removal. The tumour mass eventually reduced by 21% and was surgically excised. This is possibly the first study to use imatinib mesylate as a tumour reduction neoadjuvant to therapeutically address a feline cutaneous mast cell tumour located in a surgically inaccessible part of the body.

Keywords: feline; mast cell tumour; chemotherapy; tyrosine kinase inhibitor

A mast cell tumour (MCT) is a cancer of the white blood cells that are typically involved in inflammation and are observed in response to allergens. MCT can manifest in a cutaneous or visceral form, and is a common skin tumour in both cats and dogs (Halsey et al. 2010). MCT approximately comprises 20% of all cutaneous tumours in cats (London and Thamm 2012). Over 90% of MCTs that occur on the skin in cats are benign, whereas visceral MCTs may demonstrate a more aggressive prognosis (London and Thamm 2012). This disease is typically observed in middle-aged cats. Clinical evidence to determine the optimal treatment modality for MCTs in cats is particularly limited.

Treatment and prognosis can vary according to the tumour location and the histological classification (London and Thamm 2012). Supportive care for these patients includes the administration of glucocorticoids to reduce the inflammation and possible cytotoxic effects, along with H1 and H2 blockers, followed by treatment with antibiotics and analgesics as needed. In addition, the prognosis for cats with solitary cutaneous mast cell tumours is excellent following surgical removal (London and Thamm 2012).

Tumour reduction neoadjuvant chemotherapy includes the administration of therapeutic agents before the primary treatment. This strategy has been used to either reduce the tumour size when surgical excision with the existing tumour size is deemed impossible, or to enhance the chances of a complete histological excision (Stanclift and Gilson 2008).

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Currently, there are no studies that have specifically evaluated the efficacy of imatinib mesylate in the tumour reduction of neoadjuvant tyrosine kinase inhibitor (TKI) therapy for feline MCT. Here, we report the successful management of a feline MCT case using imatinib for the neoadjuvant TKI therapy.

Case description

A white, two-year-old, castrated, female American shorthair cat presented with an acute growth of a dermal mass in the genital area which had developed over the previous three months. The initial physical examination revealed a red, ulcerated, and swollen solitary edematous mass (about 3.0 × 2.5 cm in size) (Figure 1A). The remaining outcomes of the physical examination were unremarkable.

The complete blood count (CBC) and chemistry panel outcomes revealed that all the values, except for the triglycerides (1.94 mmol/l; range 0.11–1.13 mmol/l) and lactate (5.8 mmol/l; range 0.6–2.5 mmol/l) were within the normal reference limits. The results of the thoracic abdominal X-ray imaging showed no metastatic findings like a bone invasion, and the mass lesion was observed at the level of the subcutis through an abdominal ultrasound scanning. The results of the fine-needle aspiration (FNA) performed on the mass demonstrated numerous degranulated round cells with fine granules and anisokaryosis (Figure 2). An eight mm punch skin biopsy sample of the mass showed the following histomorphological features: occasional low mitotic indices (less than one in ten high power field) and neoplastic mast cells showing typical metachromatic purple intracytoplasmic granules after toluidine blue stain staining (Figure 3). The histopathological examination revealed that the tumour was at the level of the subcutis and was well-differentiated. The tumour cells were positively stained with toluidine blue. Based on these results, a grade I mastocytic, well-differentiated, low metastatic potential, cutaneous MCT was diagnosed.

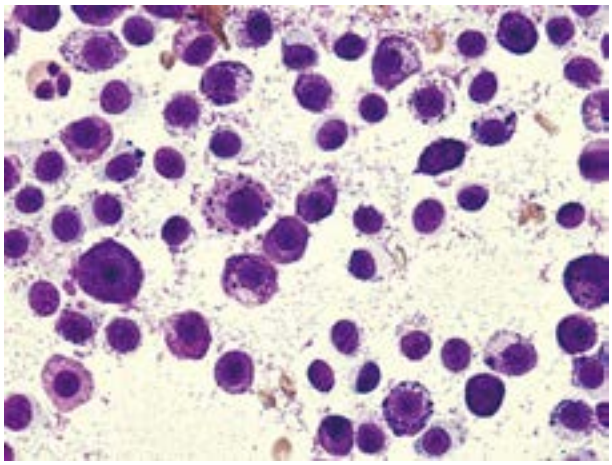

Figure 2. Cytology from a fine-needle aspirate (FNA) of the cutaneous mass lesion. The FNA of the mast cell tumour on the cat's skin showing the variable cytoplasmic granularity of the mast cells and a mild to moderate variation of cell sizes and shapes (Diff-Quik stain; magnification, × 1 000)

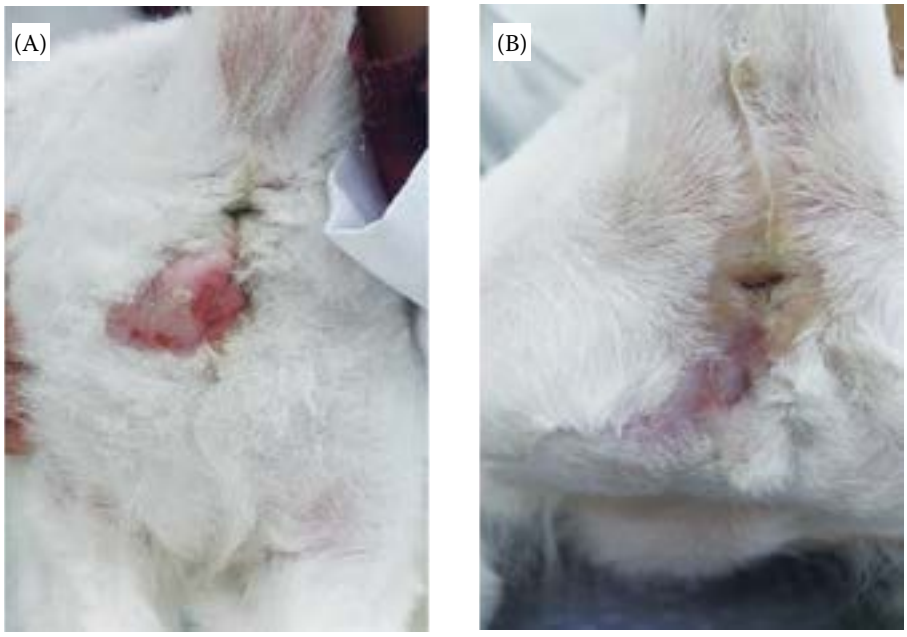

Figure 1. Cutaneous mast cell tumour. (A) A two-year-old white American shorthair cat with a solitary skin mass that was red, ulcerated, and swollen in the genital area. (B) The site of the removed cutaneous mast cell tumour three weeks after surgery. The postsurgical scar is particularly small

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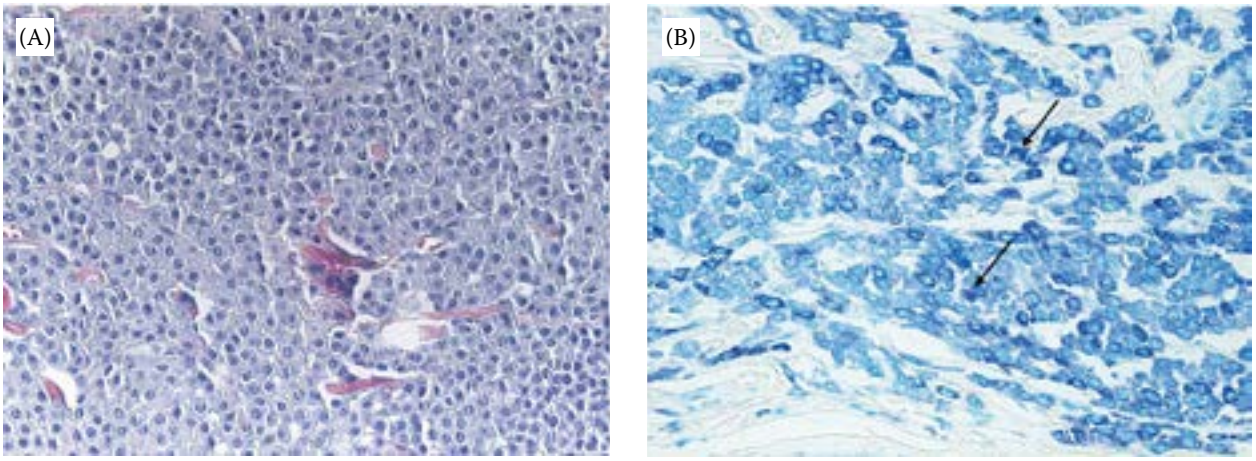

Figure 3. Histopathological image of the mast cell tumour of a cat. (A) An 8-mm punch biopsy revealed round to polyhedral tumour cells that were arranged in a dense sheet (haematoxylin and eosin; magnification × 400). (B) The neoplastic mast cells showing the typical metachromatic purple intracytoplasmic granules (arrows) (toluidine blue; magnification × 400)

The surgical removal required a resection margin of 2–3 cm; however, the lesion could not be operated on immediately in this case, considering the fact that its location included the anus and genital region. Cetirizine (Tirizin Tab; Hanmi Pharm, Seoul, Republic of Korea) (2.5 mg once daily) and famotidine (Famotidine, Hanmi Pharm, Seoul, Republic of Korea) (0.5 mg/kg twice daily) were administered orally to the cat to prevent the effects of the histamine released from the tumour cells. Additionally, prednisolone (Solondo®; Yuhan, Seoul, Republic of Korea) (1 mg/kg twice daily) was administered orally to decrease the inflammation associated with the tumour cells. There was a notable decrease in skin erythema and oedema, without any remarkable changes in the size of the mass.

Subsequently, the cat was orally treated with imatinib (Gleevec®; Novartis, Basel, Swiss), a TKI, at a dosage of 5 mg/kg twice daily. The mass reduced in size (to approximately 2.5 × 2.0 cm), followed by the elimination of the erythema and oedema; this improvement was observed ten weeks after initiating the oral medication. During this period, there were no abnormalities observed in the results of the haematological examination (including the CBC) and the serum biochemistry; furthermore, the outcomes of the physical examination were normal. The mass was then successfully removed surgically despite the narrow margins.

The surgical specimen showed that the tumour was approximately 3.0 × 2.5 cm in size, which was the maximum possible range for surgical accessibility; furthermore, it had an irregular surface and originated from the dermis in the genital area. The histological findings were identical to those observed in the previous skin biopsy. The patient had no recurrence for one year and follow-up visits, once every three months, are continuing for routine health examinations.

DISCUSSION AND CONCLUSIONS

Tyrosine kinases are cell membrane-bound growth factor receptors that can stimulate uncontrolled cellular proliferation. A mutation of the *c-kit* gene, which codes for the tyrosine kinase receptor (CD117), similar to that described in some dogs with MCTs, has been reported in 52–92% of feline cutaneous MCTs (Isotani 2010; Sabattini and Bettini 2010). A number of tumours in dogs and cats are causatively associated with this mutation of the tyrosine kinase gene. TKIs can be important in the treatment of MCT (Takeuchi et al. 2012).

Imatinib is a TKI, which is more stable than conventional chemotherapeutic agents (e.g., vinblastine and CCNU; lomustine) and is associated with a lower incidence of adverse effects (Marconato et al. 2008). This drug was specifically designed to target the constitutively active bcr-abl fusion protein found in human patients with chronic myelogenous leukemia (CML). Targeted chemotherapy using drugs including imatinib is the recommended treatment strategy for MCTs in animals, consider-

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ing the fact that TKI therapy, including that with imatinib, does not cause the progression of the usual adverse effects of chemotherapy despite the elimination or shortening of the long, drug-free periods. This is contrary to the effects observed with the administration of conventional therapeutic regimens containing agents such as vinblastine and cyclophosphamide (Isotani et al. 2008).

A recent study reported a similar response to therapy in 10/21 dogs with MCTs treated with imatinib (Isotani et al. 2008). The objective response rate was 50% in dogs with MCT, following which there were no obvious symptoms of toxicity, including hepatotoxicity (Isotani et al. 2008). Furthermore, a cat with systemic mastocytosis was reportedly treated with imatinib (10 mg/kg) (Isotani et al. 2006). These dosages of the drug induced complete responses to the therapy at five weeks of treatment without toxicity.

A previous study investigated the mutation status of the *KIT* gene in feline MCTs and examined the effects of inhibiting imatinib mesylate via phosphorylation of the mutant *KIT* gene *in vitro* and in clinical feline cases (Isotani et al. 2010). According to the study results, following two to three weeks of treatment with imatinib mesylate, clinical responses were observed in seven of the eight cats that underwent the treatment, including six partial responses and one complete response (Isotani et al. 2010).

Previously, imatinib has only been used to improve the quality of life of patients with high-grade MCT or extensive tumour metastasis. However, here, we used imatinib for a targeted therapy in a cat with a grade 0 tumour, which resulted in a significant reduction in the tumour size before surgical removal.

Surgical excision and radiation therapy are the two most successful treatment options available. Tumours that are localised and that can be widely excised should ideally be addressed via surgical intervention. A procedure that includes a 3-cm margin of the surrounding normal tissue is recommended for MCTs (Simpson et al. 2004).

In this case, the mass was located near the genitalia and anus. We aimed at reducing the tumour size as much as possible through medical treatment to ensure the surgical success. Consequently, imatinib worked well, and the response of the reduction in the tumour size to < 21% was assessed based on the RECIST (response evaluation criteria in solid tumours) guideline (Eisenhauer et al. 2009). Furthermore, this is possibly the first report of a complete treatment by tumour reduction using a neoadjuvant therapy with imatinib for feline cutaneous MCTs.

To the best of our knowledge this is the first study to use imatinib mesylate as a neoadjuvant TKI therapeutic agent to address a case of feline cutaneous MCT located in an inaccessible part of the body. Imatinib mesylate can be a palliative treatment modality for animals presenting with a tumour in an inaccessible location or a tumour for which surgery may be difficult.

Conflict of interest

The authors declare no conflict of interest.

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