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Clinical Application of Imatinib Mesylate in a Case of Feline Cutaneous Mast Cell Tumor: Clinical Progress, Histopathological, and Immunohistochemical Findings

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Abstract : A 1.5-year-old neutered male domestic short hair cat was presented with multiple nodular mass, and suspected mast cell tumor on the surface of the right ear, accompanied by submandibular lymph node involvement. Histopathological Examinations and KIT (CD117) immunohistochemical staining was performed after the surgical resection of the entire right ear pinna. This patient was diagnosed with an anaplastic mast cell tumor with a diffuse positive cytoplasmic expression of KIT. Imatinib mesylate was prescribed after surgical resection; the patient presented without recurrence or metastasis for 2 years. Mild leukopenia was observed as the only side effect of imatinib mesylate during medication.

***Key words* :** cat, imatinib mesylate, immunohistochemistry, KIT, mast cell tumor.

Introduction

Feline mast cell tumors (MCTs) are typically classified as cutaneous, visceral, and gastrointestinal forms, since the clinical features, tumor behavior, and prognosis vary depending on the organs affected (which might overlap) (9,18,19,25). Cutaneous mast cell tumors (CMCTs) are the second most common skin tumor in cats that mainly occur on the head, trunk, neck, and legs (9,20).

The present study describes a case of feline CMCT; the patient was presented with multiple nodular masses on the ear and lymph node involvement that were diagnosed using cytological, histopathological, and KIT immunohistochemical analyses. The cat was successfully treated with surgery and tyrosine kinase inhibitor (TKI).

Case

A 1.5-year-old neutered male domestic short hair cat was presented to a local animal hospital with an early symptom of rashes on the surface of the right ear, which began 9 months before presentation. The rashes proliferated over the right ear, accompanied by enlarged submandibular lymph node on the right side. The masses on the ear were tentatively diagnosed as cutaneous mast cell tumor (CMCT) based on the cytological examination using fine-needle aspiration (Fig 2A). A significant number of mast cells were also observed on the right submandibular lymph node (Fig 2B).

The case was referred to our hospital to establish a definitive diagnosis and provide appropriate treatment. A solitary, firm, raised, dome-shaped mass approximately 1 cm in diameter was observed grossly on the ventral surface of the right external ear pinna; other small, round, and firm nodules were also observed throughout the dorsal surface of the right pinna (Fig 1A and 1B). The right submandibular lymph node was found enlarged on palpation.

The biochemical testing of blood detected the presence of leukopenia ($3.9 \times 10^9/l$; reference range, $5.5\text{-}19.5 \times 10^9/l$). Blood and buffy coat smears revealed eosinophilia, although we could not find mast cells in both samples. There were no significant changes in the serum biochemical profiles. The coagulation tests revealed a prolonged activated partial thromboplastin time (aPTT, 153 sec; reference range, 94-125 sec); however, prothrombin time (PT) was found within the reference range.

Radiographic and computed tomographic scans revealed a mildly enlarged right submandibular lymph node without metastasis in other areas of the head and thoracic cavity. Cytological examination by bone marrow aspiration showed no remarkable abnormalities. The entire right ear pinna was removed surgically (Fig 1C and 1D) and examined histopathologically. Proliferated mast cells with pleomorphic cytoplasm and nucleus were identified using hematoxylin and

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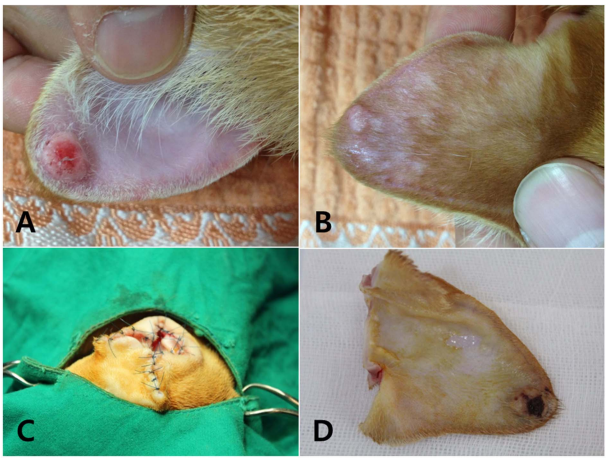

Fig 1. Gross findings and surgical procedure images of the patient. A solitary, firm, raised, dome-shaped mass approximately 1 cm in diameter on the ventral surface of the right external ear pinna (A), and small, round, and firm nodules spread on the dorsal surface (B). The entire right ear pinna removed surgically (C and D).

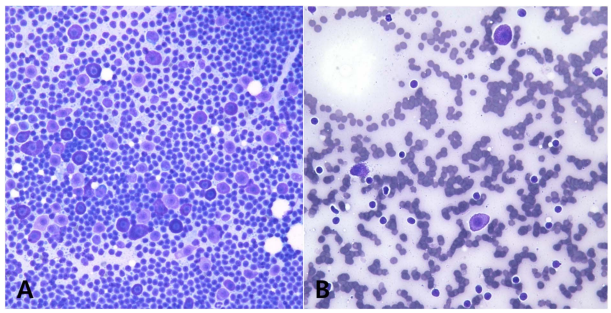

Fig 2. Fine needle aspiration cytological results of the patient. Mast cells with abundant granules are observed on cytological examinations of ear (A) and submandibular lymph node specimens (B). Diff Quik staining (× 400).

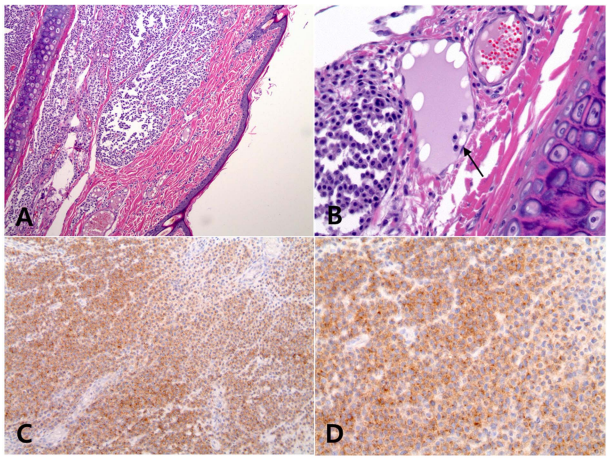

Fig 3. Histopathological and immunohistochemical findings from the patient. Proliferated mast cells with pleomorphic cytoplasm and nucleus are highly invaded in the connective tissues (hematoxylin and eosin staining, A: × 200, B: × 400). Mast cells are observed in the lymphatic vessel (B: black arrow). Predominantly diffuse cytoplasmic expression of c-Kit can be seen in mast cells (c-Kit staining, C: × 200, D: × 400).

eosin staining. We observed that the tumoral mast cells highly invaded the connective tissues that circumscribed poorly, and inflammatory cells such as neutrophils and eosinophils infiltrated the lesions (Fig 3A). Mast cells were also found invading the lymphatic vessels, which might also metastasize to regional lymph nodes (Fig 3B). Hence, the present case of the CMCT was classified histologically as an anaplastic mastocytic form. c-Kit (A4502, 1:300, DAKO, Carpinteria, CA) immunohistochemical staining was performed for prescribing chemotherapy after surgery to prevent relapse or dissemination into the lymphatic system. The c-Kit analysis of tumoral mast cells showed a predominantly diffuse positive cytoplasmic expression, as well as partial positive membranous expression (Fig 3C and 3D). Based on the results, the diagnosis was confirmed as feline anaplastic CMCT with aberrant cytoplasmic KIT localization.

We prescribed imatinib mesylate (Gleevec®, Novartis, Basel, Switzerland; 10 mg/kg, q24h, PO) and prednisolone (Solondo®, Yuhan Medica, Seoul, Korea; 1 mg/kg, q24h, PO) to the patient. Prednisolone was tapered gradually as the size of lymph node decreased. Mild leukopenia was the only side effect of imatinib mesylate observed during the period of medication. All medications were stopped eventually when the cat became healthy, as confirmed on the basis of the results obtained from regular blood tests, radiography, and abdominal ultrasonography as well as patient's general condition (6 weeks after initial prescription). The cat presented without recurrence or metastasis for 2 years after surgical and medical treatments.

Discussion

Several reports have described the histopathological or immunohistochemical characteristics of MCTs that can help predict prognosis and apply specific treatments for individual MCTs (10-12,19,27). Histopathological and clinical features such as mitotic index, Ki67 expression, AgNOR expression, lymph node involvement, clinical signs, or metastasis are regarded as good prognostic factors for MCTs (2,18,21, 26,27,29,30,32,34). In human and canine medicine, over the last 20 years, *c-kit* mutation has been a significant prognostic marker for MCTs or systemic mastocytosis (6,8,17,33,35). Type III receptor tyrosine kinase (KIT or CD117) is encoded by *c-kit* proto-oncogene. This protein is located on the cellular membrane to bind ligands and plays a significant role in the development, proliferation, metastasis, and survival of mast cells; hence, *c-kit* mutation is associated with oncogenesis (7). Normal mast cells show mild membranous KIT expression with immunohistochemical staining, whereas mast cells with the *c-kit* mutation tend to have cytoplasmic KIT distribution and show significant correlation with high histological grade and a worse prognosis in dogs (4,13,19,22,35).

In cats, the cytoplasmic KIT expression has been reported in approximately 67% of CMCTs (24). However, the previous studies revealed that KIT localization was not associated with histological features in feline CMCTs. Moreover, another

study identified that the correlation between c-kit mutation and KIT localization was not statistically significant, although 73% of feline CMCTs with *c-kit* mutation expressed cytoplasmic KIT, as compared to 33% of membranous KIT expression (28).

KIT expression has been used as an indicator for performing chemotherapeutic intervention using tyrosine kinase inhibitors (TKIs) in MCTs. There are two studies that suggest the TKI, imatinib mesylate, as a targeted anti-neoplastic agent in feline MCTs (10,11). Moreover, imatinib mesylate has also shown a positive effect in 8 out of 10 cats with MCTs in the skin, spleen, or liver, although not all cats showed *c-kit* mutation (11).

Unfortunately, no general consensus regarding the staging system for feline MCTs exists. According to several previous studies, the following features occur predominantly in cats with MCTs: histologically diffuse and pleomorphic tumors, multiple nodular lesions, or primary visceral tumors (1-3,15,18). The present patient was guarded clinically considering these factors. The present case of CMCT was identified as stage III (multiple dermal tumors with large infiltration, with or without regional lymph node involvement), based on the World Health Organization's staging system that includes criterion such as lymph node involvement, metastasis, and clinical signs. A study performed by Lister and Sorenmo (2006) in 41 cats with CMCT revealed a significantly shorter survival time in patients presenting with stage III (15). If MCTs are highly expected to be malignant, as observed in this patient, additional aggressive treatments, such as radiation therapy or chemotherapy combined with surgical removal, are recommended (10,11,23,31). Therefore, we chose imatinib mesylate based on the KIT expression observed after surgery; the treatment subsequently resulted in good prognosis and caused only few side effects.

TKIs are relatively novel chemotherapeutic drugs that act as target-specific tyrosine kinases. These types of drugs exert significant clinical benefits in veterinary medicine (16). Although masitinib and toceranib toxicities such as gastrointestinal irritation or myelosuppression were observed in cats, they are generally well-tolerated (5). Imatinib mesylate is also a known, well-tolerated agent in cats that causes minimal gastrointestinal toxicity (as observed in a prior study) and mild leukopenia (as observed in the present case) (14). In the present case, imatinib mesylate showed a favorable response for CMCTs with KIT expression. Survival time of this patient was found to be longer than the mean survival time (582 days) of patients with similar feline MCTs as observed in a previous study (15). Prednisolone is usually less effective in feline MCTs as compared to canines; however, it was used to alleviate inflammation in the present case (18). Concomitant treatments with prednisolone did not contribute to the suppression of feline MCTs, as observed in a study regarding imatinib mesylate (11).

In summary, we encountered a feline CMCT case, which was suspected to be an aggressive tumor, and showed cytoplasmic KIT expression. Treatment with imatinib mesylate was effective and the patients showed good prognosis. A combination of histopathological analysis and KIT expression evaluation may provide a reasonable evidence to manage feline CMCTs using novel therapeutic options such as TKIs. Additional studies are needed to evaluate the benefits and side effects of TKIs for a long duration, in a large population.

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