A case with feline restrictive orbital myofibroblastic sarcoma treated with toceranib as adjuvant chemotherapy

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Abstract

A 7-year-old American short-haired cat was presented with blepharospasm in the right eye. The case was finally performed with orbital exenteration, leading to the diagnosis of feline restrictive orbital myofibroblastic sarcoma. Adjuvant chemotherapy with toceranib was given for one month after surgery. However, the case died four months after surgery.

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Running head: Feline restrictive orbital myofibroblastic sarcoma treated with toceranib (66 characters)

ABSTRACT

A 7-year-old American short-haired cat was presented with blepharospasm in the right eye. The case was finally performed with orbital exenteration, leading to the diagnosis of feline restrictive orbital myofibroblastic sarcoma. Adjuvant chemotherapy with toceranib was given for one month after surgery. However, the case died four months after surgery.

KEY WORD: adjuvant chemotherapy, feline orbital tumor, feline restrictive orbital myofibroblastic sarcoma, toceranib

Introduction

Most orbital diseases are caused by infection, inflammation, or neoplasia, and malignant orbital tumors are common in dogs and cats.[1, 2] In dogs, various types of tumors with different origins occur in the orbit, including mesenchymal origin, epithelial origin, and miscellaneous origin.[2] In cats, in contrast, epithelial tumors such as squamous cell carcinoma and round cell tumors such as lymphoma are more common orbital tumors, while mesenchymal tumors are less common.[3] In recent years, there are some reports of a rare orbital mesenchymal tumor called feline restrictive orbital myofibroblastic sarcoma (FROMS), with clinical characteristics of eyelid restriction leading to exposure keratitis without formation of an orbital mass.[4-8] However, detailed data of this tumor including the origin and tumorigenesis has not been elucidated.

Surgical resection is often selected as the first choice in the treatment of orbital tumors in dogs and cats.[2, 9]Other treatment options include radiation therapy and chemotherapy, which may be performed after surgery as adjuvant therapy.[9, 10] In dogs with orbital tumor, cases with malignant orbital tumor treated with orbitotomy followed by adjuvant radiation therapy and chemotherapy have been reported.[1] However, the efficacy of postsurgical adjuvant therapy for dogs and cats remains unclear due to a paucity of clinical reports on adjuvant therapy.[10]

The use of molecular targeted drugs, one type of chemotherapy, has been reported in veterinary medicine.[11-13] Toceranib, which is one of the molecular target drugs, is a tyrosine kinase receptor inhibitor and has been shown to inhibit KIT, platelet-derived growth factor receptor, and vascular endothelial growth factor receptor.[14-16] Clinical use of toceranib in cats for the treatment of mast cell tumors[17, 18], adenocarcinoma[19, 20], gastrointestinal stromal tumor[21], pancreatic carcinoma[22], mammary carcinoma[23], squamous cell carcinoma[24-26], and feline injection site-associated sarcomas (FISS)[27] has been reported. However, the number of these reports in cats is fewer compared with that in dogs. In addition, there are no reports of adjuvant chemotherapy using molecular target drugs for FROMS. Herein, we present the first report of using toceranib as postsurgical adjuvant chemotherapy for the treatment of FROMS in a cat.

Case presentation

A seven-year-old neutered male American shorthair cat was referred to the Saitama Animal Medical Center with symptoms of blepharospasm in the right eye. Ophthalmic examination revealed superficial corneal ulceration with mild eyelid restriction in the right eye, but no abnormality was observed in the left eye (Figure 1). Treatment with antibiotic and hyaluronate eye drops was started, but the corneal ulceration in the right eye did not improve at follow-up three weeks later. In addition, entropion caused by eyelid restriction persisted. Partial right eyelid tarsorrhaphy was performed to treat the corneal ulcers. However, vision was eventually lost in the right eye due to severe exposure keratitis caused by complete eyelid restriction, and resistance to retropulsion of the globe was observed at follow-up. Orbital disease was suspected from these clinical findings. Ultrasound examination was performed, but no apparent mass was observed in the globe or in the orbit. (Figure 2A). Oral prednisolone (5 mg/head, once daily) was prescribed for suspected orbital inflammation but was ineffective, and the dose was tapered off and eventually discontinued.

Given the lack of improvement in clinical symptoms by medical treatment, surgical resection following computed tomography (CT) was scheduled on day 138 after initial presentation. CT revealed a space-occupying lesion in the right orbit, with infiltration extending from the eyelid to the lips (Figure2B). There were no osteolytic lesions in the orbital bone and no sign of abdominal or thoracic metastasis. Following the CT examination, orbital exenteration of the right eye was performed. The orbit contained multiple nodular lesions, and these were removed to the extent possible. All specimens were fixed in 10% formalin, embedded in paraffin, sectioned at 4 μm, and subject to hematoxylin and eosin (HE) and immunohistochemical staining.

Histopathological examination of HE stained sections revealed the proliferation of atypical spindle tumor cells infiltrating the skeletal muscle in the orbital tissue with thin collagenous materials between spindle cells and moderate lymphoplasmacytic cell infiltration (Figure3A), but there was no invasion into the globe. Neoplastic spindle cells resemble reactive fibroblasts or myofibroblasts with mild anisocytosis and anisokaryosis. These spindle cells have a moderate amount of elongated eosinophilic cytoplasm and ovoid nuclei with finely stripped chromatin and one to two nucleoli. There were 4–5 mitotic figures in tumor cells per ten high-power fields. Immunohistochemistry showed positive staining for smooth muscle actin (SMA) in the tumor cells (Figure3B). Based on these histopathological findings, the tumors were diagnosed as FROMS.

After surgery, the mass in the right lip enlarged, leading to feeding difficulty. A gastrostomy tube was placed under general anesthesia. Three weeks after surgery, toceranib 2.17 mg/kg was initiated three times per week as adjuvant chemotherapy. Toceranib administration was continued for one month. However, the residual tumor continued to increase in size, and adjuvant chemotherapy was deemed ineffective and was discontinued. Subsequently, bleeding from the tumor occurred, which severely deteriorated the cat's quality of life. Eventually, the cat died four months after surgery, 257 days after initial presentation.

Discussion

At first presentation, the cat showed corneal ulcers and exposure keratitis caused by eyelid restriction. Despite medical therapy, the clinical symptoms deteriorated, and CT images demonstrated an orbital mass. Orbital exenteration was performed, and histopathological examination revealed the presence of spindle tumor cells. After surgery, toceranib was administrated due to enlargement of the residual mass. This is the first report of using toceranib as adjuvant chemotherapy for treating FROMS in a cat.

Feline orbital neoplasms are commonly diagnosed in clinical practice[28]. Isaza et al. [3] reported the incidence of various types of orbital tumor in cats as follows: round cell tumors 47%, epithelial tumors 38%, mesenchymal tumors 13%, and neurologic origin tumors 1%. In their report, the most common diagnoses were lymphoma and squamous cell carcinoma. Among the mesenchymal tumors, FROMS was reported most frequently, and other malignant tumors including fibrosarcoma, osteosarcoma, unspecified sarcoma, and spindle cell tumors were also reported.[3]FROMS has unique clinical characteristics marked by eyelid restriction without discrete orbital mass formation. Based on these characteristic findings, this disease was previously considered to be an inflammatory disorder, but was re-defined as a neoplastic lesion by Bell et al. in 2011.[4] FROMS is known to originate from the orbit and actively invades connective tissues of the orbit including eyelids and conjunctiva.[4, 7] Cases of the tumor invading the contralateral eye causing bilateral symptoms have also been reported.[6] Histopathology examination of FROMS shows infiltrative proliferation of low-grade atypical spindle cells with collagen matrix in the orbit and substantia propria of conjunctival tissue.[4] Immunohistochemistry of FROMS shows positive staining for S100, vimentin, and alfa-SMA (αSMA).[4]From these histopathological findings, FROMS is suspected to originate from myofibroblast cells. On the other hand, fibrosarcoma is a malignant tumor originating from fibrous connective tissue and typically consists of highly atypical spindle cells with abundant mitosis. Feline fibrosarcoma usually forms a large mass with a strong infiltrate into the adjacent tissues. Other orbital mesenchymal tumors in cats, including osteosarcoma and spindle cell tumors, show various degrees of differentiation.[3] In our case, proliferation of fibroblast-like spindle cells was observed by histopathological examination, leading to a high suspicion of mesenchymal tumor. In addition, positive staining for αSMA suggested that the tumor was derived from myofibroblasts. These findings were consistent with the histopathological features of FROMS. Regarding clinical presentation, findings such as eyelid restriction and the lack of discrete orbital mass at the initial

ultrasound examination were also consistent with the clinical features of FROMS. Hence, The final diagnosis was made as FROMS. However, the mitotic count in this case was relatively high compared with previous reports. These differences from previous reports may imply the existence of subtypes of FROMS.

Regarding treatment, surgical resection is often selected as the first option for feline orbital tumors. As most orbital tumors in cats are malignant, frequent local recurrence and metastasis are a clinical issue.[29] Therefore, surgical resection together with other effective treatments are needed to control the progression of the disease. Additional treatment following surgery is called adjuvant therapy. Adjuvant therapy includes radiotherapy and chemotherapy. Some purposes of adjuvant radiotherapy have been proposed, including curative and palliative intent. In a previous study that evaluated adjuvant radiotherapy for FISS, a finely fractionated radiotherapy protocol significantly prolonged the survival time compared with a coarse fractionated radiotherapy protocol.[30] Regarding adjuvant chemotherapy in cats, doxorubicin and lomustine have been reported for FISS, and both anti-cancer drugs demonstrated tumor suppression.[31, 32] In the present case, toceranib was selected as adjuvant chemotherapy. Since the tumor was considered highly malignant due to the rapid enlargement, we planned therapy according to the evidence-based treatment for FISS, which is also a mesenchymal tumor. Radiation therapy was not selected due to the lack of facilities at our clinic, and frequent procedures under anesthesia could lead to further deterioration of the cat's general condition. Regarding chemotherapeutic agents, doxorubicin is known to have adverse effects including gastrointestinal and renal toxicity[31], and lomustine has been reported to cause severe leukopenia leading to dose reduction.[32] Considering the poor general condition of the cat, use of doxorubicin or lomustine was challenging due to the possibility of severe side effects. Therefore, we considered using molecular targeted drugs that are effective for sarcoma with mild adverse effects.

In recent years, molecular target drugs such as imatinib, masitinib, and toceranib have been used in veterinary medicine.[11]Toceranib has been shown to inhibit KIT, platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor, and tumor growth.[13-16] Katayama et al. reported that inhibition of PDGFR suppressed feline fibrosarcoma in *in vitro*experiments.[33] Holtermann et al. treated FISS cases with toceranib as adjuvant therapy, but observed no significant tumor reduction.[27] Holtermann et al suggested that toceranib may be potentially effective to some extent because all specimens of FISS were positive for PDGFR in immunohistochemistry. They also reported that gastrointestinal toxicity was the main adverse effect of toceranib, but all symptoms were mild and temporary, and improved after discontinuation of toceranib. In the present case, toceranib was administered at a dose of 2.17 mg/kg three times per week for one month, but the residual tumor enlarged and invaded connective tissues. The response to toceranib treatment was considered poor, and there was no noticeable tumor suppression effect. Some factors may account for the lack of effectiveness. First, toceranib may be ineffective for this tumor type. Since the origin of this tumor has not been identified, and molecular biological characterization remains unknown, it is unclear whether toceranib affects this tumor type. Second, the long interval between surgery and toceranib administration may be a factor. Since toceranib was administered three weeks after surgery and the tumor had already progressed, the effect of tumor suppression may not be fully demonstrated. Third, the dosage may be low. In previous reports, toceranib was used in the range of 1.6 to 3.5 mg/kg.[17, 27, 34, 35] Since the general condition of the cat was deteriorating, toceranib was used at a lower dose compared with previous reports. Therefore, the effective blood concentration of toceranib needed to suppress tumor growth might not be reached. This cat manifested restriction of the eyelids and exposed keratitis at initial presentation without obvious mass lesion in the orbit by ultrasound examination, which led to a delay in performing surgical intervention. Some orbital mesenchymal tumors in cats, such as FROMS, progress rapidly and are already advanced at the time of deciding surgical intervention, making it challenging to perform radical resection. Therefore, early surgical treatment should be considered when findings in cats suggest an orbital tumor as in the present case. In addition, adjuvant therapy should also be considered due to local recurrence and metastasis. Although toceranib did not suppress the tumor in this case, early administration or higher doses might have some effect on it\sout.

In conclusion, this is the first case report of treatment with toceranib as postsurgical adjuvant chemotherapy for FROMS. Further study to examine the dosage and timing of toceranib administration is warranted.

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Conflict of interest

All authors declare that they have no competing interests.

Authors contribution

H.K. wrote the first draft of the manuscript. A.U., Y.K., and K.R. contributed to the clinical diagnose and treatment. Y.S. contributed to histopathological evaluation. H.K., Y.K., and N.T. contributed to critical discussion of this case report. All authors reviewed the manuscript, approved the submission, and agreed to be accountable for all aspects of this work.

Consent

All authors were conducted in accordance with the code of ethics of the Japan Veterinary Medical Association, and written informed consent was provided from the owner.

Data availability statement

The data that support the findings of this study are available from the corresponding author, H.K., upon reasonable request.

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Figure Legend

Figure 1. Clinical findings of the cat during the clinical course. (A) At initial presentation, blepharospasm in the right eye was observed. (B) On day 19, corneal ulceration at dorsal site did not improve, and restriction of the eyelids was prominent. (C, D) On day 75, exposure keratitis in the right eye deteriorated due to persisting eyelid restriction, and resistance to posterior ocular compression was observed.

Figure 2. Imaging findings. (A) On day 75, Ultrasound examination detected no obvious mass in both the globe nor in the orbit. (B) On day 138, A computed tomography scan revealed a high intensity space-occupying lesion in the orbit of right eye (*).

Figure 3. Histopathological findings of the tumor. (A) Hematoxylin-eosin staining showed proliferation of bland spindle cells with moderate collagen matrix. (B) Immunohistochemical staining showed moderate cytoplasmic labeling of smooth muscle actin in spindle tumor cells. Scale bar = 200 μm (100×).

Figure 1. Komatsu H et al.

Figure 2. Komatsu H et al.

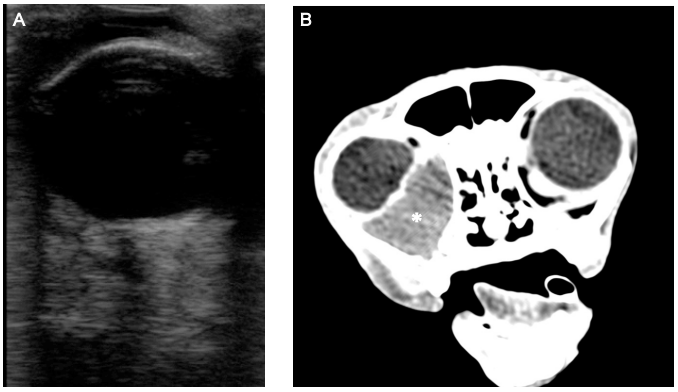

Figure 3. Komatsu H et al.