NOTE *Internal Medicine*

Imatinib Mesylate plus Hydroxyurea Chemotherapy for Cerebellar Meningioma in a Belgian Malinois Dog

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ABSTRACT. An 8-year-old intact male Belgian Malinois, weighing 37.2 kg, was referred for evaluation due to right side facial paresis, ataxia and a 2-month history of decreased cognitive ability. Physical and neurological examinations revealed mild depression, left-sided head tilt, right-sided facial paresis and ataxia. A well-demarcated, broad-based cerebellar mass and hyperostosis were found on CT imaging of the brain. Based on these CT findings, a cerebellar meningioma was strongly suspected. Hydroxyurea and prednisolone were administered; after 4 weeks, there was reduction in mass size as compared to initial CT results. However, the mass size was found to have grown 6 weeks after hydroxyurea treatment. We then prescribed a combination of imatinib mesylate and hydroxyurea. Two weeks following combination treatment, the mass size had reduced significantly. The mass continuously decreased in size until the patient died during anesthesia. Cerebellar transitional meningioma was confirmed by histopathologic examination. To the author's knowledge, this is the first reported case of imatinib mesylate plus hydroxyurea therapy for the treatment of meningioma in veterinary medicine.
KEY WORDS: canine, hydroxyurea, imatinib mesylate, meningioma, tyrosine kinase inhibitor

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An 8-year-old intact male Belgian Malinois, weighing 37.2 kg, was referred to the Gyeongsang National University Animal Medical Center for evaluation of right-sided facial paresis, ataxia and a 2-month history of decreased cognitive ability. The patient had no history of exposure to toxins or head trauma as well as no prior medical problems. Physical and neurological examinations showed mild depression, left-sided head tilt, right-sided facial paresis and ataxia. Complete blood counts and serum biochemical examinations, radiography and urinalysis were unremarkable. A computed tomography (CT) scan (Somatom Emotion Duo, Siemens AG, Munich, Germany) of the brain was performed to rule out a structural brain lesion. Pre- and post-contrast CT images were taken. The right dorsal cerebellum contained a mass with peripheral contrast enhancement and an internal hypoattenuating lesion. The mass was extra-axial, round and smoothly marginated. The mass had a broad base along the right tentorium cerebelli, which appeared thickened when compared to the left adjacent bone (Fig. 1A). These findings were most consistent with a meningioma of the cerebellum. Results of the CSF analysis indicated an increased nucleated cell count of 48 cells/μl (reference range, 0–5 cells/μl), and cytological examination showed monocytoid cell population. Based on the results of the CT scan and CSF analysis, the patient was tentatively diagnosed with a cerebellar meningioma.

Management with prednisolone (Prednisolone®, Korea Pharma, Seoul, Korea; 1 mg/kg, per oral twice in a day) and hydroxyurea (Hydrin®, Korea United Pharm., Seoul, Korea; 50 mg/kg, per oral every other day) was initiated with gradual improvement in clinical signs [7, 10, 15]. CT images were evaluated at presentation and 4, 10, 12 and 18 weeks after initial treatment to assess the patient's response to therapy. Four weeks after initial treatment, ataxia and facial paresis had improved. A CT was performed, and all images were retrieved to the Lucion image post processing system (Infinitt Technology, Seoul, Korea). The volumes of the mass in the post-contrast images were then measured with the auto-tracking tool. When compared to the initial CT result (Fig. 1A; 8.47 cm^3), cerebellar mass size was significantly reduced in the 2nd CT (4 weeks post-treatment) (Fig. 1B; 4.27 cm^3). Prednisolone and hydroxyurea administration were continued; however, mild ataxia and depression reoccurred 6 weeks after the 2nd CT. The 3rd CT (10 weeks post-treatment) indicated an increase in mass size (Fig. 1C; 6.56 cm^3). We suggested new chemotherapeutic trial to the owner, and it was accepted. Imatinib mesylate (Glivec®, Novartis, Stein, Switzerland; 8 mg/kg, per oral once in a day) was then added to the prednisolone and hydroxyurea therapy. Two weeks after initiation of the imatinib plus hydroxyurea therapy, neurological signs improved, and the 4th CT (12 weeks post-treatment) indicated a significant decrease in

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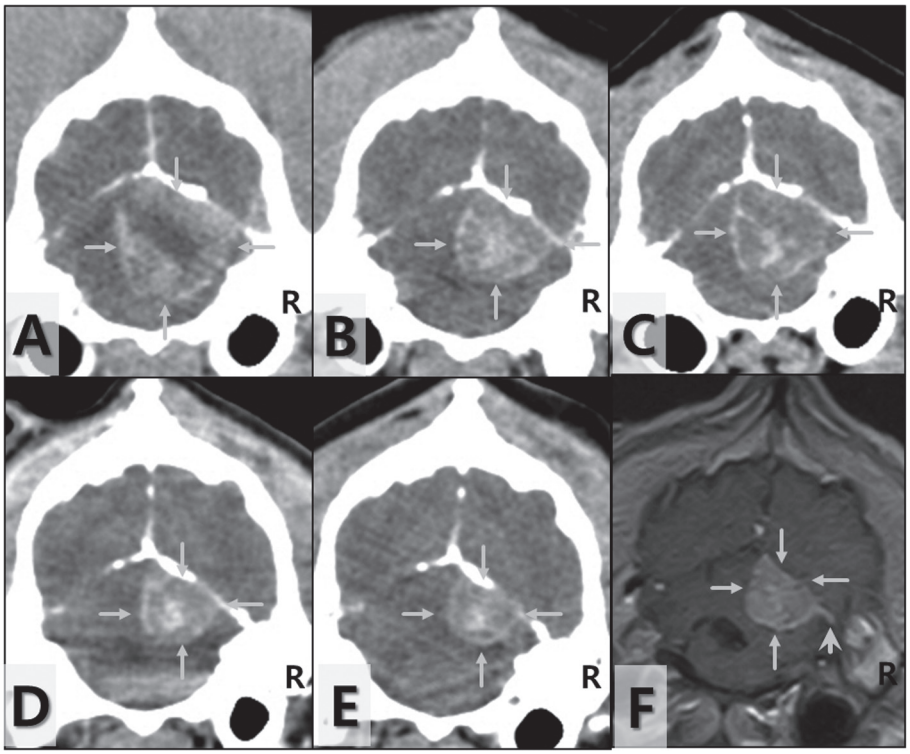

Fig. 1. Serial post-contrast CT images (A to E) and MR image (F) after chemotherapy. A) At presentation (mass volume was 8.47 cm^3), B) 4 weeks (4.27 cm^3) and C) 10 weeks (6.56 cm^3) after initial treatment of prednisolone and hydroxyurea. D) 2 weeks (3.26 cm^3) and E) 8 weeks (2.63 cm^3) after initiation of the imatinib and hydroxyurea. F) Post-contrast T1-weighted MR image 10 days after last CT examination (panel E) showed a dural tail sign (short arrow).

mass size (Fig. 1D; 3.26 cm^3). We maintained the imatinib plus hydroxyurea therapy for 6 weeks and then reevaluated mass size. The 5th CT (18 weeks post-treatment) showed a decrease in mass size (Fig. 1E; 2.63 cm^3). Ten days following this CT examination, MR images of the brain (APERTO 0.4, Hitachi Medical Co., Tokyo, Japan) were obtained that revealed that the mass had marked contrast enhancement with a focal hypointense area within. The mass appeared to extend along the dura, and the surrounding meninges appeared thickened (Fig. 1F). Unfortunately, the patient arrested during anesthesia and expired. Because the patient was well controlled under chemotherapy with imatinib plus hydroxyurea, we suspected that the patient died with sudden cardiac and respiratory depression during general anesthesia.

On necropsy, a well-defined mass was located in the right cerebellar region (Fig. 2A and 2B). Based on histopathological findings, the present patient was definitively diagnosed with transitional cerebellar meningioma (Fig. 2C). Platelet-derived growth factor receptors (PDGFR)-α rabbit anti-human polyclonal (aa1035-1053) antibody (LifeSpan Bioscience, Seattle, WA, U.S.A.) was used to identify the expression of PDGFR in the meningioma. Immunohistochemistry for PDGFR-α demonstrated positive staining in the cytoplasm and perinuclear dot-like pattern in the spindle cell arranged in a whorl (Fig. 2D).

Meningioma is the most common primary brain tumor in dogs [10]. Generally, treatment for canine meningioma patients entails surgery, radiation therapy, chemotherapy or combination therapy [1, 4–8, 10, 15, 17]. Most meningiomas in human medicine are treated surgically, and recurring tumors are treated with radiation therapy and repeated surgical resection [10]. Surgery and/or radiation therapy are also common typical therapeutic procedures in veterinary medicine [1, 4, 8, 10]. However, there are times when surgery or radiation therapy is not an option in canine meningioma cases, because of the deep location of the tumors, patient age, costs, ethical reasons or other complicated diseases [10]. For those patients, medical therapy, such as corticosteroids, antiepileptic drugs and chemotherapeutic agents can provide a good quality of life and prolong survival times. There were few reports of chemotherapy for meningiomas in veterinary medicine until recently [5–7, 17]. According to previous reports, hydroxyurea and lomustine showed beneficial effects for meningioma in both human and veterinary patients [5, 7, 10, 16, 17].

Most of the meningiomas, regardless of grade, express PDGFR [13, 18]. Some meningiomas also express platelet-derived growth factors (PDGF) [13, 18]. Furthermore, PDGFR expression is also increased in some brain tumors, such as glioma, glioblastoma mutiforme and ependymoma

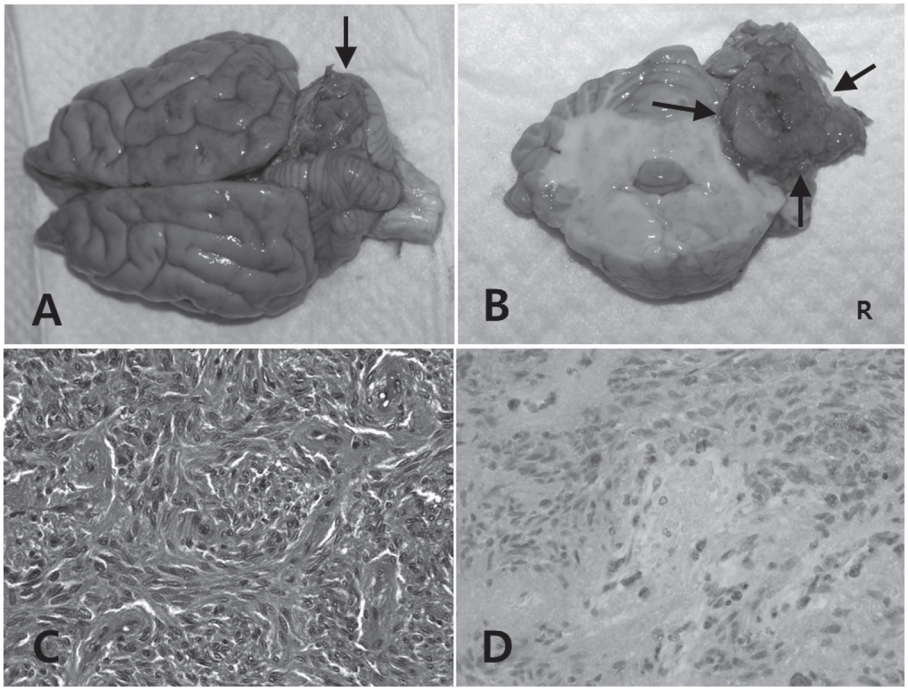

Fig. 2. Necropsy, histopathological and immunohistochemical findings of the present case. A well-defined mass is located in the right cerebellar area (A and B; arrows). Histopathology indicated transitional meningioma (C). Spindle and polygonal tumor cells are observed, and concentric whorl patterns predominate (C: × 400). Immunohistochemistry for PDGFR-α demonstrated positive staining in the cytoplasm and perinuclear dot-like pattern in the spindle cell arranged in a whorl (D: × 600).

[2, 3, 12, 14]. Imatinib mesylate is known as an inhibitor of PDGFR, Bcr-Abl, c-KIT and c-Fms tyrosine kinase [9, 13, 18]. Recently, several reports demonstrated that imatinib mesylate could be a treatment option for various brain tumors [2, 3, 12–14, 18]. In veterinary medicine, imatinib mesylate has been used in some dogs and cats to treat mast cell tumors or vaccine-associated sarcomas [9]. The recommended dose of imatinib mesylate is 5–10 mg/kg per oral once in a day [9]. In the present case, we tentatively diagnosed cerebellar meningioma and started treatment with a steroid and hydroxyurea. According to one previous report [15], tumor cases treated palliatively (especially tumor located in cerebellum, pons or medulla) had a poor prognosis. Although a few reports [7, 11, 16, 17] indicated that hydroxyurea could be a good treatment option in meningioma cases, in our experience, some meningioma cases did not show a response. The tumor size reduced significantly after 4 weeks of hydroxyurea therapy in the present case. However, the tumor increased in size, and clinical signs worsened despite maintenance of hydroxyurea therapy. One previous report [18] insisted that combination therapy with imatinib mesylate and hydroxyurea could be more effective in meningiomas when compared to single imatinib mesylate therapy. We decided to use this combination therapy of imatinib mesylate and hydroxyurea and achieved a good result. The present patient expired during anesthesia and therefore, showed a relatively shorter survival time. However, this case demonstrated the beneficial effect of imatinib mesylate plus hydroxyurea therapy in cases with cerebellar meningioma.

To the author's knowledge, this is the first reported case of the use of imatinib mesylate plus hydroxyurea therapy for meningioma in veterinary medicine.

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