pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 36(2) : 109-111 (2019)
http://dx.doi.org/10.17555/jvc.2019.04.36.2.109

Journal of Veterinary Clinics
www.ksvc.or.kr

Application of a Cyclooxygenase Inhibitor and Itraconazole for Pulmonary Squamous Cell Carcinoma in a Dog

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(Received: October 18, 2018 / Accepted: February 24, 2019)

Abstract : A dog with anorexia, cough, and regurgitation was referred to clinic. Diagnostic imaging revealed a solitary mass involving the right cranial and middle lung lobes, compression of the cranial vena cava, and deviation of the heart and mediastinum toward the left side because the mass. The mass was diagnosed as a squamous cell carcinoma via fine needle aspiration. Ten days later, the tumor was larger and the clinical signs were more severe. A combination of piroxicam and itraconazole was administered to control the mass. Two weeks after initiating this treatment, the tumor size decreased and the clinical signs improved significantly.

Key words **:** dog, itraconazole, piroxicam, pulmonary squamous cell carcinoma.

Introduction

In dogs, pulmonary squamous cell carcinoma is a rare primary tumor with high metastatic potential, and its prognosis is worse than for other lung cancers (7,11,12). Surgery, radiotherapy or chemotherapy are recommended to treat pulmonary tumors. However, in some cases, these therapeutic modalities are very limited.

In humans, squamous cell carcinoma of the lung is common (4), and thus, continuous efforts to treat this cancer have been applied. Since tumor growth and progression are dependent on tumor-associated angiogenesis, antiangiogenic therapy is considered a very effective strategy (2,7). Piroxicam and itraconazole have been used as anti-inflammatory and antifungal agents for a long time, respectively. However, recently, these drugs have received attention as antiangiogenic and antitumor agents in humans with several types of lung cancer, and not only pulmonary squamous cell carcinoma (1,6,13,14).

This case report describes the use of piroxicam and itraconazole for canine pulmonary squamous cell carcinoma, which is rare in dogs, and this combination is the first application in veterinary clinics per the authors' knowledge.

Case

A 12-year-old castrated male Shih-Tzu with cough, anorexia, and regurgitation was referred to our clinic. The cough began 3 months prior, when heart failure was diagnosed at a local hospital. Physical and blood examinations yielded no remarkable findings. There was no cardiac murmur. Upon thoracic radiography, a right cranial lobe pulmonary mass was revealed, while the heart size was normal (Fig 1A). On computed tomography (CT), a soft-tissue attenuating solitary mass involving the right cranial and middle lung lobes was observed. The mass resulted in compression of the cranial vena cava, and the heart and mediastinum were deviated towards the left caudal side. Ultrasonography-guided fine needle aspiration (FNA) of the thoracic mass was performed, and the mass was identified as a squamous cell carcinoma (Fig 2). Upon FNA examination, cells were revealed to be generally clumped and closely attached together, suggesting that they originated from epithelial cells. Each cell had the appearance of squamous epithelial cells, characterized by a flat shape and intercellular bridges. In addition, the cells presented with moderate anisokaryosis, prominent nuclei, scant cytoplasm, a high nucleus-to-cytoplasm ratio, and cytoplasmic vacuoles.

Ten days after the first visit, the owner opted for a right pulmonary lobectomy and revisited the hospital with the patient. During that period, the dog was administered with an anti-inflammatory drug, a bronchodilator from a local clinic. However, since the dog had severe cough and anorexia, he was re-evaluated using further diagnostic imaging analyses. The thoracic radiographic scans indicated that the pulmonary tumor was larger than that observed during the previous examination (Fig 1B). CT scans also revealed that the tumor extended to the left cranial thoracic cavity, resulting in the collapse of the left cranial lung lobes, and left caudal deviation of the heart and mediastinum. Furthermore, the cranial vena cava was compressed more severely and metastasis to the lymph nodes was suspected.

The owner decided against surgical intervention, and medical treatment was initiated. Since the patient's condition had exacerbated and the owner was reluctant to attempt chemotherapy, alternative medications were chosen. The patient was administered the following oral medications: piroxicam (0.3 mg/kg/day), itraconazole (20 mg/kg/day), gastric protec-

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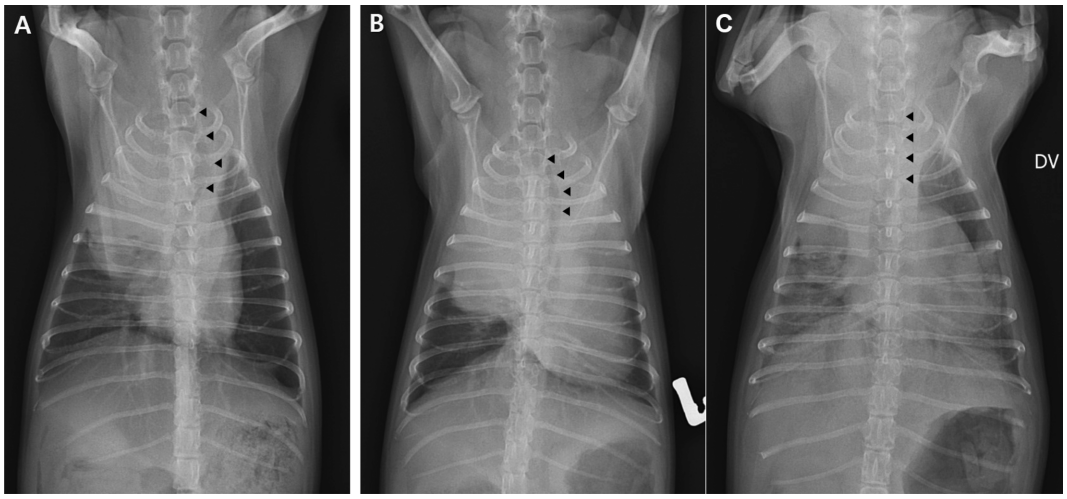

Fig 1. Ventral dorsal view of the thorax. (A) Radiography obtained upon admission reveals a primary pulmonary mass on the right cranial side. (B) Ten days after the first visit, radiography reveals that the mass enlarged compared to that in the previous image. (C) Taken 17 days after administering the oral medication (the day the patient died), the radiography reveals that the mass appeared smaller in size than before, and the trachea and mediastinum had returned to their normal position with pulmonary edema. ◀; trachea position.

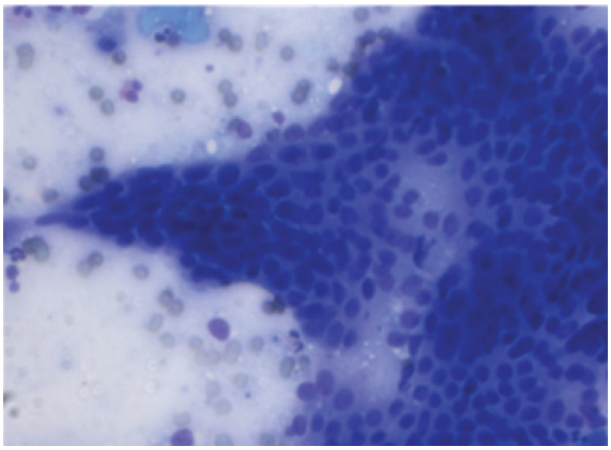

Fig 2. Images acquired from fine needle aspiration examination. Cells were generally clumped and closely attached together, suggesting these cells originated from epithelial cells. Each cell had the appearance of squamous epithelial cells, which are characterized by a flat shape and intercellular bridges.

tive agents and a bronchodilator.

One week after receiving the oral medication, the owner reported that the patient still presented with a persistent cough, although there was some improvement. Two weeks after receiving the oral medication, the patient re-visited the clinic for a check-up. The patient's condition had improved, and both the duration and frequency of coughing had decreased significantly. His appetite had also increased, and no regurgitation was observed. Upon radiological testing, the tumor size appeared smaller than before, while mild pulmonary edema was suspected, resulting from compression of the cranial vena cava. Thus, additional diuretics were prescribed. Two days later, the pulmonary edema of the patient worsened. Despite aggressive treatment, the patient died the next day. A radiograph is presented in Fig 1C.

Discussion

In dogs, pulmonary tumors are well-recognized because the cancer cells are carried by the bloodstream into the lung tissue. However, compared to lung cancer in humans, primary lung cancers are much less common, accounting for 1% of all cancers diagnosed in dogs (5). Most primary lung cancers are carcinomas that originate from the airway epithelium (5,11). The frequency of squamous cell carcinoma, one of the primary lung cancers, is 6% in dogs, which is in sharp contrast to its high frequency in men, in whom squamous cell carcinoma is the predominant type of carcinoma (4,11). This type of lung cancer is a rare primary tumor with high metastatic potential, and its prognosis is worse than for other lung cancers (7,11,12).

To treat a pulmonary tumor, surgery, radiotherapy or chemotherapy are recommended. However, in some cases, these therapeutic modalities are very limited. A tumour with associated lymph node metastasis cannot be removed by a surgical procedure. Radiotherapy is difficult to implement because there are very few centres that have the necessary facilities for its administration. Finally, most pet owners are reluctant to administer chemotherapy.

In humans, the classification of pulmonary carcinoma is more detailed. Lung carcinoma is divided into small cell lung carcinoma (SCLC) and non-SCLC (NSCLC). NSCLC is any type of epithelial lung cancer other than SCLC, and pulmonary squamous cell carcinoma is a type of NSCLC. As mentioned earlier, squamous cell carcinoma of the lung is common in humans and thus, continuous efforts to treat this cancer have been applied (12).

Since tumor growth and progression are dependent on tumor-associated angiogenesis, antiangiogenic therapy is considered a very effective strategy (2,7). Itraconazole has been used as an antifungal agent for a long time. However, recently, it has received attention as an antiangiogenic and antitumor agent. While the effects of itraconazole as an anticancer agent

in dogs have not yet been proven, in humans, some studies have demonstrated that a high dose of itraconazole (two or three times the standard antifungal dose) has antitumor effects in humans with several types of tumors, not only NSCLC (1,8,13).

Piroxicam, another drug indicated for the present patient, is a cyclooxygenase (COX) inhibitor that limits the production of prostaglandins. Generally, this drug is used to relieve pain and inflammation. However, piroxicam is also used to limit tumor growth, although the mechanism is still unclear (15). In veterinary medicine, piroxicam has been used for treating dogs with several types of cancers, including oral squamous cell carcinoma, although there are no reports of its use in pulmonary squamous cell carcinoma (3,9,10). However, there are some reports suggesting that COX inhibitors induce apoptosis in human NSCLC cell lines (6,14).

In this case, since the rate of tumor progression was so rapid and the patient's state had worsened, common agents were administered as oral medications instead of a surgical procedure and chemotherapy, based on the owner's choice. Although long-term monitoring was not feasible in our case, after oral medication, the size of the lung tumor decreased; simultaneously, the clinical signs improved significantly and the owner's satisfaction was very high. Itraconazole and piroxicam are low-cost drugs with minimal toxicity, and are easily accessible, compared to other anticancer drugs. Thus, the combination of piroxicam and itraconazole may be used for canine pulmonary squamous cell carcinoma palliatively.

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