Chemotherapy of Mammary Comedocarcinoma with Doxorubicin in a Dog

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Abstract An 11-year-old, intact female, Miniature Poodle presented with an abdominal mass. The abdominal mass was located around the right fifth mammary gland. The surgically removed mammary mass was subjected to histopathological examination. Based on the microscopic interpretation, a final diagnosis of an intermediate grade infiltrative mammary comedocarcinoma was established. Computed tomography for metastasis evaluation after surgical resection of the tumor showed enlarged right medial iliac and right inguinal lymph nodes, and a micro-nodule in the accessory lung lobe, suggesting metastasis of the mammary gland tumor. Doxorubicin, a chemotherapeutic drug, was administered six times at three week intervals. However, despite chemotherapy, the masses around the fourth and fifth mammary gland on the right side enlarged in size, and the treatment was discontinued at the request of the owner. The anticancer response to mammary comedocarcinoma is poor and the patient is in hospice management. This is the first attempt to treat a case of canine mammary comedocarcinoma in South Korea.

Key words mammary comedocarcinoma, doxorubicin, mammary gland tumors, canine.

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Introduction

Mammary gland tumors (MGTs) are one of the most common tumors in female canines that are mostly primary, and originate from glandular or supporting structures (3). The incidence of MGTs varies in different countries owing to the recent increase in surgical neutering. Histopathological examination is the gold standard for the diagnosis of MGT. According to the histological classification of 2011 canine MGTs can be classified as benign or malignant (2). Benign MGTs include various forms of adenomas, myoepitheliomas, and complex adenomas. Epithelial tumors are the most common form of malignant MGTs; these include carcinoma in situ, simple carcinoma, solid carcinoma, comedocarcinoma, anaplastic carcinoma, and complex carcinoma (1,2). Comedocarcinoma is an independent classification system since it was previously included in carcinoma-in situ, and is histologically characterized by the presence of a necrotic site in the center of the tumor cell aggregates (2). Surgical excision is considered the gold standard for treating MGTs. Although little is known about the effectiveness of chemotherapy, it is still recommended as a postoperative treatment option in canines with highly malignant metastatic MGTs with poor prognosis (1).

In this report, we describe a case of mammary comedocarcinoma in a dog treated with doxorubicin. To our knowledge, this is the first case where chemotherapy was attempted in a canine mammary comedocarcinoma patient in South Korea.

Case Report

An 11-year-old, intact female Miniature Poodle, weighing 4.85 kg was presented to the local animal clinic for the eval-

Fig. 1. Surgically resected mass around the 5th right mammary gland.

A

B

C

Fig. 2. (A) Numerous mammary glands and ducts showed moderate to severe multifocal proliferation of lining epithelium. The centers of the nodular foci often consist of necrotic cellular debris (caseous necrosis, comedo pattern) (N). H&E, ×40. (B) Neoplastic cells had round to oval nuclei with prominent nucleoli, scant basophilic cytoplasm and some mitosis because of heavy proliferation of lining epithelial cells with multiple layers. H&E, ×400. (C) Lymphatics containing tumor cell emboli (arrow) inside the lumen and invasion of adjacent connective tissue of tumor cells. H&E, ×400.

uation of an abdominal mass. The abdominal mass was located around the fifth mammary gland on the right side and was 1 cm × 2 cm in size.

Complete blood count (CBC) and serum biochemistry tests did not reveal any significant findings. At chest and abdominal radiography, there were no additional specific findings other than abdominal tumor. Due to owner refusal, no additional tests such as fine-needle aspiration or tumor metastasis assessment were performed, only lumpectomy and ovariectomy were performed. Histopathologic examination of the surgically resected mammary mass was performed (IDEXX Laboratories, USA) (Fig. 1).

Histopathologically, the sample contained haired skin, subcutis, and mammary tissue. Microscopic evaluation revealed neoplastic mammary nodular foci, often consisting of necrotic cellular debris (comedo pattern) (Fig. 2A). The neoplastic cells had small to moderate amount of cytoplasm, irregularly shaped round to ovoid nuclei with stippled chromatin, and one or two nucleoli. There was a moderate variation in nuclear size and shape (Fig. 2B). The neoplastic cells showed a strong invasive tendency to adjacent connective tissues;

therefore, many lymphatics contained neoplastic cell emboli in their lumens (Fig. 2C). Based on the histopathological findings, a final diagnosis of grade II infiltrative mammary comedocarcinoma was established. The patient was referred to the Veterinary Medical Teaching Hospital of Chungnam National University to assess tumor metastasis.

In the examination performed 18 days after the surgery, physical examination revealed enlargement of the right inguinal lymph node. Serum chemistry profile revealed an increase in the levels of alanine transaminase (153 U/L, reference range 19-70 U/L), gamma-glutamyl transferase (10 U/L, reference range 0-6 U/L), and blood urea nitrogen (28.4 mg/dL, reference range 8-26 mg/dL). Abdominal ultrasonography showed right medial iliac lymph node enlargement, gallbladder sludge, and bilateral nephrolithiasis. No specific findings were detected on urinalysis. Computed tomography (CT) was performed to evaluate the degree of MGT metastasis. The CT images displayed enlarged right medial iliac lymph node. The lymph node parenchyma was heterogenous, oval to round in shape, and showed a contrast enhancement effect (Fig. 3). The right inguinal lymph node was also enlarged (8.2 mm

Fig. 3. Pre-contrast (A) and post-contrast (B) transverse CT images of right and left medial iliac lymph nodes. CT showed that the right lymph node (arrow) was enlarged compared to the left side, and the parenchyma was heterogenous and had a contrast-enhancing effect.

Fig. 4. CT image of caudal lung lobe. One ground-glass nodule (arrow) is observed on the ventral side of the right caudal lung lobe.

× 6.7 mm × 7.0 mm), and exhibited a homogenous parenchyma and a weak contrast enhancement effect. Increased interstitial pattern density and parenchymal bands due to ground-glass opacity were observed in the right cranial and middle lobes of the lung window, and a ground-glass nodule was observed on the ventral side of the right caudal lobe (Fig. 4). A circular micronodule with clear margins having a diameter of approximately 1.3 mm was observed in the caudodorsal part of the accessory lung lobe. No enlargement of the intrathoracic lymph nodes was observed. Based on the CT findings, it was suspected that the tumor had metastasized to the intraabdominal lymph nodes and lungs.

Doxorubicin (Doxorubicin inj. 0.2%; Teva-Handok; 1 mg/kg, intravenous infusion for 20 min) was administered six times at three week intervals. Electrocardiography and echocardiography performed prior to doxorubicin administration did not reveal any pre-existing heart disease. CBC examination was performed each time before chemotherapy. Maropitant citrate (Cerenia; Zoetis, USA; 1 mg/kg subcutaneous), dexamethasone (Jeil Dexamethasone Injection; Jeil Pharm, S. Korea; 0.2 mg/kg subcutaneous), and chlorpheniramine maleate (Chlorpheniramine Maleate Injection Huons; Huons, S. Korea; 0.5 mg/kg subcutaneous) were administered as pre-medications. Maropitant citrate (2 mg/kg, orally daily) was prescribed as a home medication for 5 days to prevent delayed vomiting seen after doxorubicin administration. During chemotherapy, the patient experienced gastrointestinal symptoms, such as intermittent vomiting and diarrhea. However, no other side effects were observed. Three weeks after the last chemotherapy session, a CT scan was scheduled to evaluate the tumor response to anticancer drugs. However, a physical examination performed before the CT scan confirmed two firm and movable masses that were previously invisible around the fourth and fifth mammary glands on the right side. Thoracic radiography did not show any specific changes in lung parenchyma compared to previous tests, nor did it show enlargement of the thoracic lymph nodes. Ultrasonography revealed two abdominal tumors with increased vascularity and a heterogeneous parenchyma. At the request of the owner, no additional tests and treatment were performed. Four months after the tumor recurred, the patient is in hospice management and is alive.

Discussion

According to the 2011 classification of canine mammary tumors, comedocarcinoma is characterized histologically by a multinodular appearance, with a well-demarcated necrotic center surrounded by neoplastic cells (2,7). Infiltration of

neoplastic cells into the lymph vessels can be found in the periphery of the tumor, with metastasis to regional lymph nodes (2). In this case, the histopathological findings of the resected mass were typical of comedocarcinoma, and invasion of the tumor cells into the surrounding lymphatic vessels was found. Based on these findings, a diagnosis of infiltrative mammary comedocarcinoma was established. It was classified as a grade II carcinoma on the basis of tubule formation, nuclear pleomorphism, and the number of mitoses in the high-power field. In a cohort study of 229 dogs with canine mammary tumors based on histological subtypes, only 17 of the 229 dogs were identified as comedocarcinoma. And of the 17 dogs, the local metastasis rate was 6% (1/17) and the distinct metastasis rate was 82% (14/17) (4). In this patient, CT findings showed peri-mammary lymph node enlargement and lung nodules, suggesting a high probability of MGT metastasis. The abdominal mass detected at the same site after chemotherapy was considered to be a local recurrence. After identification of the new MGTs no further investigations were carried out at the request of the owner. Although it is unclear, we believe that the tumor recurred because a clear margin of ≤ 1 mm was seen on histological examination of the previously removed mass, and no surrounding mammary glands and lymph nodes were resected. At the local animal clinic, metastasis evaluation was not performed at the request of the patient's owner, and only lumpectomy was performed with the hope of removing the tumor only. If metastasis was evaluated by CT at the time of the first visit and total or partial mastectomy was performed instead of lumpectomy, it is considered that better results were obtained.

There is limited data on the efficacy of chemotherapy for the treatment of MGTs in dogs. Although most medical treatments are experimental, chemotherapy is routinely recommended in dogs with "high-risk" tumors despite these uncertainties. This is because, surgery alone is not adequate in treating large histologically aggressive tumors with suspected lymph node metastasis. Some studies have reported that anticancer drugs alone, or chemotherapy with different combinations of anticancer drugs and nonsteroidal anti-inflammatory drugs (NSAIDs) have shown improved results (1,7). Commonly used drugs include doxorubicin, carboplatin, mitoxantrone, 5-fluorouracil, and cyclophosphamide (6).

In veterinary medicine, there are limited reports on the treatment of mammary comedocarcinoma, and no concrete anticancer treatment protocols have been established. In this case, chemotherapy was done using doxorubicin, which is often used in the treatment of mammary tumors in canines. A previous study showed no significant difference in the re-

currence-free interval, time to metastasis, and overall survival time when doxorubicin was administered as an postoperative adjuvant drug in dogs with invasive malignant MGTs (5). The therapeutic response of some anti-cancer agents to canine mammary tumor was reported to be of little significance, but there were cases where it was reported that there was a therapeutic response to doxorubicin (8). In addition, since doxorubicin is generally used as the first-line protocol for the treatment of human breast cancer, anticancer treatment using doxorubicin was started (7). We then decided to evaluate the therapeutic response to doxorubicin and, if there was no response, consider additional treatment options such as cyclophosphamide and tyrosine kinase inhibitors. Carboplatin and nonsteroidal anti-inflammatory drugs was not selected as an anticancer drug due to concerns about renal dysfunction when considering the patient's muscle mass and creatinine values. However, in this patient, the tumor did not respond to anticancer treatment with doxorubicin. Since the patient has a new lesion confirmed, canine response evaluation criteria in solid tumors indicates that the overall response is progressive disease. During the six anticancer treatments, the patient's physical examination showed no recurrence of new mass, and no other specific findings were observed in intermittent chest radiation and abdominal ultrasound. This could not be suspected of mass progression and metastasis. Since the treatment of the dog was discontinued at the request of the owner, no alternate chemotherapeutic drugs could be administered and the suspected metastasis of MGT could not be confirmed.

In a cohort study, 17 dogs diagnosed with mammary comedocarcinoma histopathologically had 14 months median survival time and 18 months mean survival time. The 1-year survival rate of these dogs was 71% (12/17) and the 2-year survival rate was 29% (5/17) (4). In this case, the patient is in hospice management without any particular problems until now, 9 months after the diagnosis of the patient's mammary comedocarcinoma and 4 months after the recurrence of the mass was confirmed.

This is the first reported case of anticancer treatment in a

canine with mammary comedocarcinoma in South Korea. Further studies are needed to develop effective anticancer therapeutic strategies and chemotherapy protocols in canine mammary comedocarcinoma patients.

Conflicts of Interest

The authors have no conflicting interests.

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