NOTE *Internal Medicine*

Palliative Intravenous Cisplatin Treatment for Concurrent Peritoneal and Pleural Mesothelioma in a Dog

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ABSTRACT. A 10-year-old Maltese dog was presented with abdominal distention and dyspnea. Cytological examination of pleural and peritoneal effusion was suggestive of malignant effusion of glandular origin. Numerous, multifocal, tan to white nodules were disseminated throughout the surface of the abdominal organs and peritoneum at biopsy. Histologically, the tumors were revealed to be an epithelial type of mesothelioma. Neoplastic cells co-expressed cytokeratin and vimentin. Intravenous administration of cisplatin was chosen as the treatment. During treatment, the dog's overall body condition improved and the clinical signs were relieved without significant side effects. The survival time from diagnosis to sudden death by unknown cause was 153 days.
KEY WORDS: canine, cisplatin, mesothelioma.

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Mesothelioma is a rare tumor arising from the mesothelium of the serous lining of the pleural, pericardial, and peritoneal cavities or tunica vaginalis of the testis [1, 7, 11]. In dogs, the main clinical signs result from the accumulation of fluid in body cavities. This tumor has distinct histologic patterns, including the epithelioid, sarcomatoid or sclerosing, and biphasic types [3, 7]. An effective standard treatment protocol for mesothelioma has yet to be formulated. Currently, radical excision, pericardiectomy, and some chemotherapeutic agents have been the treatments of choice to palliate and slow the progression. Recently, administration of intravenous and intracavity cisplatin have been attempted as treatments for mesothelioma [8, 10]. This report concerns the case of a dog with concurrent peritoneal and pleural malignant mesothelioma treated with intravenous cisplatin for palliative purposes.

A 10-year-old spayed female Maltese dog was referred to the Veterinary Teaching Hospital, Seoul National University, Korea, with a 3-month history of abdominal distension, anorexia, exercise intolerance, and dyspnea. The most prominent physical finding was abdominal distension with a palpable fluid wave. The thoracic and abdominal radiographs confirmed pleural and peritoneal effusion. A sternal lymphadenopathy was identified on the thoracic radiographs. Serosanguinous fluid was removed from both the peritoneal and pleural spaces by centesis. The dog's complete blood cell count showed mild neutrophilia (22.2×10^3; reference limits, $6.0–17.0 \times 10^3$). Abnormalities on the serum chemistry profile included mild hypoalbuminemia (2.6 g/d*l*; reference limits, 2.8–4.5 g/d*l*) and hypoproteinemia (4.8 g/d*l*; reference limits, 5.0–7.2 g/d*l*). Smears of both the pleural and peritoneal fluids revealed a predominant population of epithelial cells mostly in clusters. Some cells were glandular in appearance with extracellular eosinophilic material. The cells had a mild to moderate amount of moderately basophilic and indistinctly marginated cytoplasm, sometimes with distinct vacuoles. The nuclei were round, oval to elongated, and hyperchromatic with one or two prominent nucleoli. Anisokaryosis was moderate. Rare inflammatory cells were found. These finding were suggestive of neoplastic effusion of either adenocarcinoma or mesothelioma (Fig. 1). This dog was readmitted for exploratory laparatomy 3 days later. The abdominal cavity contained about 300 m*l* of serosanguineous fluid. Numerous, multifocal to often confluent, 4–10 mm wide, tan to white firm nodules were disseminated throughout the surfaces of the pancreas, omentum, small intestine, mesentery, spleen, and peritoneum. The lesions of the peritoneum were multifocally erosive and a confluent mass was observed in the dorsal region of the peritoneum adjacent to the right lateral liver lobe where hemodiapedesis was also observed.

Several nodules disseminated on the serosal surface were removed and submitted for histopathology. Histologically, the nodules consisted of neoplastic mesothelial cells with papillary outgrowth that was supported by fibrous connective tissue. The neoplastic cells were cuboidal and polyhedral in shape, contained round to oval hyperchromatic nuclei, and occasionally formed glandular structures (Fig. 2). The degree of mitotic index was low (0 to 2 in a 400 × high power field). For Immunohistochemical analysis, the following antibodies were applied to samples sections: cytokeratin (DAKO, Carpinteria, CA, U.S.A., clone MNF 116) and vimentin (DAKO, Carpinteria, CA, U.S.A., clone V9) at 1:200 dilutions labeled using the standard avidin-

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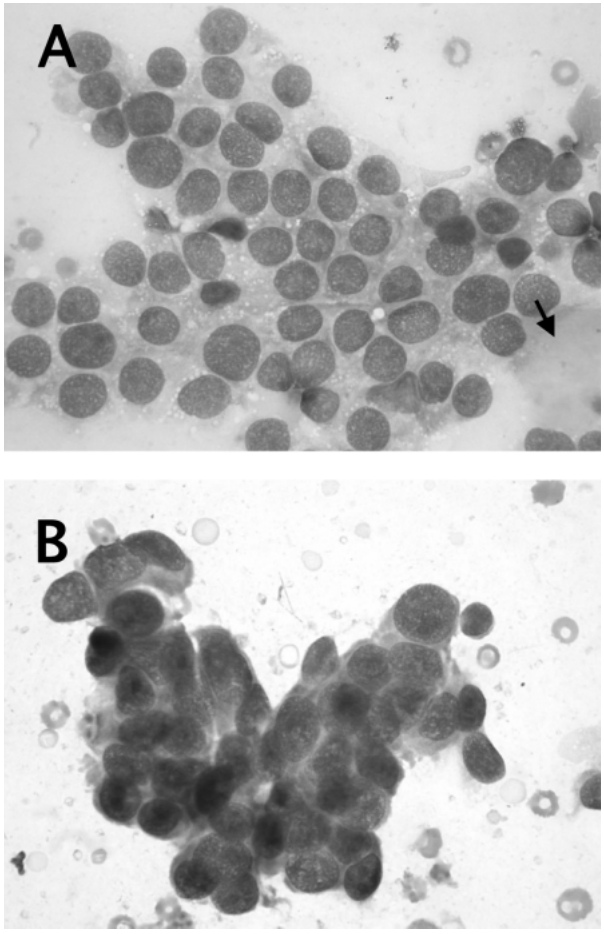

Fig. 1. Cytology of the canine mesothelioma. Peritoneal effusion (A): Note the presence of a sheet of neoplastic cells with vacuolated, weakly basophilic cytoplasm and hyperchromatic, granular nuclear chromatin. Anisokaryosis is moderate. Arrow=The extracellular pink material associated with the sheet of cells. Diff-Quik stain, ×1000. Pleural effusion (B): A tight cluster of epithelial cells with a scant amount of basophilic cytoplasm is found. The nuclei are hyperchromatic and round to oval with more than one prominent nucleoli. Diff-Quik stain, × 1,000.

biotin-peroxidase (ABC) technique (Vector Lab, Burlingame, CA, U.S.A.). The neoplastic cells were positive for both cytokeratin and vimentin (Fig. 3). Based on these findings, this case was diagnosed as a concurrent peritoneal and pleural epithelial type mesothelioma.

This dog was treated with 5 cycles of cisplatin (50 mg/m^2, Korea United Pharm Inc., Seoul, Korea) every 3 weeks intravenously with 8-hr saline diuresis. An intramuscular (IM) injection of 0.4 mg/kg of butorphanol was administered as an antiemetic 20 min before the cisplatin treatment. Saline was administered before and after the cisplatin treatment to induce diuresis. Hemograms were monitored immediately before and at 7 to 10 days after chemotherapy administration. Blood urea nitrogen (BUN), serum creatinine concentrations, and urine specific gravity (USG) were

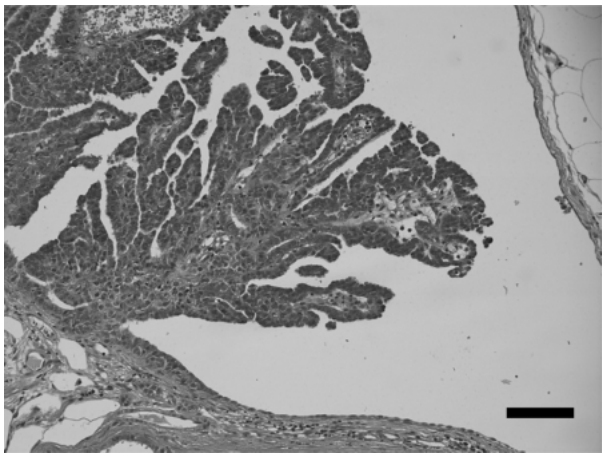

Fig. 2. Canine mesothelioma. Note papillary outgrowth of the neoplastic mesothelial cells with good fibrous connective tissue support. H&E. Bar = 500 μm.

measured immediately before cisplatin administration. Following this therapy, the dog had complete remission of its clinical signs for 100 days after initiation of the chemotherapy. The dog regained its appetite and the dyspnea was relieved after the second treatment. During chemotherapy, no clinical signs of toxicity were observed. Fifty three day after starting chemotherapy, the volume of ascites was remarkably decreased and the sternal lymph node size was decreased on thoracic and abdominal radiographs. The left cranial lung lobe was consolidated and no respiratory signs were observed. After 6 cycles of treatment, the dog suddenly died. However, the exact cause of its sudden death was unknown since necropsy was not permitted. The total survival time was 153 days from the time of diagnosis until death.

Mesotheliomas are rare in dogs, and thus understanding of the tumor's behavior and prognosis is limited. A strong association has been suggested between mesothelioma and asbestos in dogs based on detection of fibers in the lungs of the affected animals [5]. Mesotheliomas should be differentiated from peritoneal spreading of abdominal primary carcinomas. In this case, the intense immunoreactivities for both keratin and vimentin seems to support the diagnosis of mesothelioma [13].

No satisfactory treatment protocol exists for mesothelioma [9]. Surgical resection, radiotherapy, and chemotherapy can be used as treatment options. In humans, treatment of mesothelioma is only considered palliative with generally poor responses [16]. In the human field, cisplatin therapy is considered the most appropriate single agent chemotherapy for mesothelioma [12]. Cisplatin alone demonstrated an overall response rate of 14% in patients with diffuse malignant mesothelioma [14]. Combination therapeutic challenges with cisplatin have been reported, but no regimen has emerged as the standard for mesothelioma. Chemotherapy is usually the treatment of choice due to the distribution of

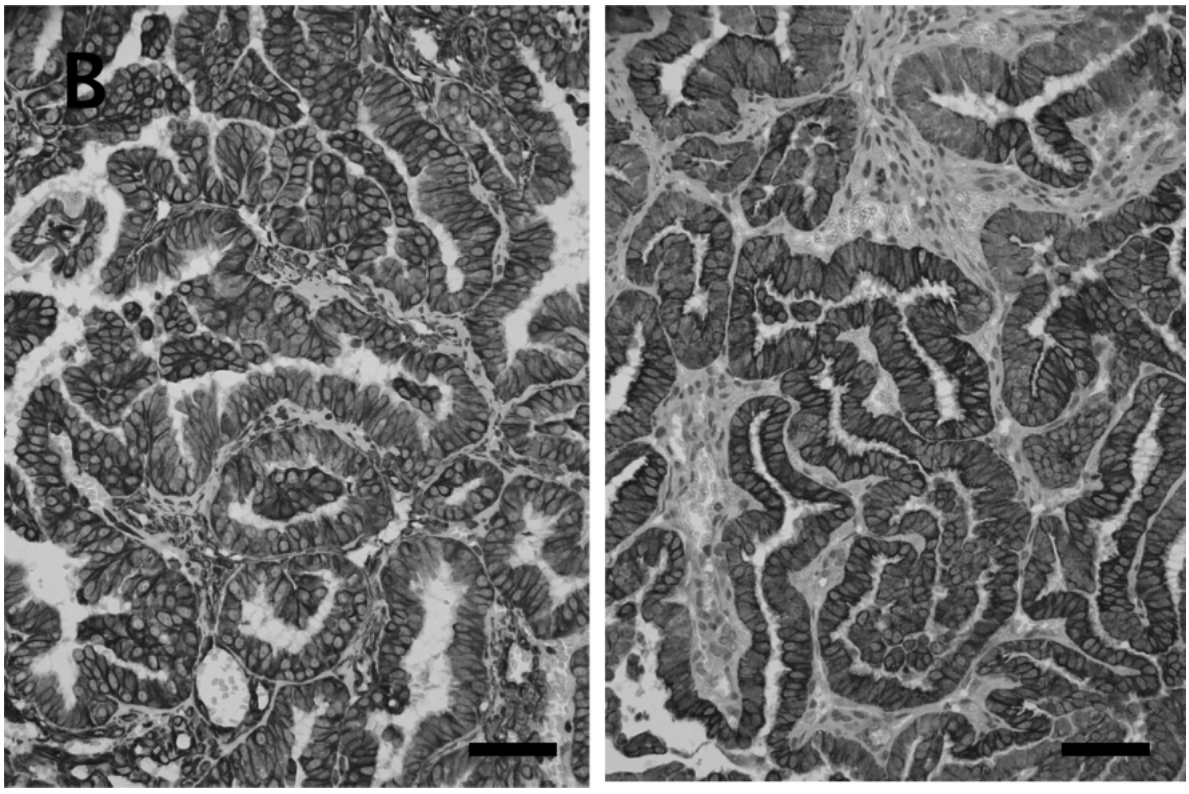

Fig. 3. Canine mesothelioma. Note that the neoplastic cells are strongly positive for cytokeratin (A) and vimentin (B). ABC method. Bar = 100 μm.

the lesions and tissue toxicities. However, no single agent or combination of drugs has yielded satisfactory results for mesothelioma in dogs [13]. Treatments with intracavitary platinum drugs have been reported in canine mesotheliomas [6, 8, 10, 13]. Dogs treated with intrathoracic and intravenous cisplatin or intravenous doxorubicin remained free of disease for 27 months [2]. In another report, a dog survived for 300 days after a doxorubicin and intracavitary cisplatin treatment [15].

In this case, we elected to offer intravenous cisplatin as a trial therapy for the dog because the tumor lesions were widespread (peritoneal and pleural). A biopsy sample was only obtained from the abdominal space; however, we suspected concurrent pleural involvement due to cytology results being the same (Fig. 1). Based on the knowledge of tumor biology and prognosis, this treatment was not given with curative intent, but with the hope of providing palliation and increased quality of life.

Nausea and vomiting are common side effects of cisplatin chemotherapy, and most of the reported cases of these side effects occurred during or following treatment [4]. Use of antiemetic drugs is effective for preventing nausea and vomiting. In this case, intramuscular butorphanol was given before cisplatin administration and metoclopramide was provided for home use as an antiemetic agent; no significant nausea or vomiting was observed. Nephrotoxicity is cumulative and often dose-limiting. To prevent nephrotoxicity, diuresis with 0.9% saline was performed, and the serum creatinine and USG were evaluated before each cisplatin administration. In this case, no changes were detected in serum creatinine USG during treatment.

On the basis of the complete remission of clinical signs observed following the cisplatin treatment, improved appetite and activity, and lack of side effects associated with the treatment, we conclude that palliation was achieved; although it was temporal. The intravenous cisplatin is worth of consideration for management of mesothelioma.

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