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CASE REPORT

Undifferentiated Hepatic Pleomorphic Sarcoma (Malignant Fibrous Histiocytoma) in a Dog: A Case Report

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A B S T R A C T

A 3.5-year-old neutered female, Alaskan Malamute, dog was presented to our hospital with a primary complaint of recurrent vomiting. A liver mass was observed on radiography and ultrasonography; however, gastroscopy was seemingly not associated with the vomiting. Computed tomography (CT) scan confirmed compression of the gastric pylorus due to enlarged liver lymph nodes, which was then determined to the cause of the vomiting. In addition, a round nodule was present in the spleen, with suspected lung, intrathoracic and intraperitoneal lymph node metastasis. Histopathologic examination of the liver mass biopsy showed malignant histiocytes. Furthermore, immunohistochemistry staining using Vimentin, Iba-1, alpha-smooth muscle actin (α-SMA), and Masson's Trichrome staining confirmed that the neoplastic cells were of histiocyte and myofibroblast origin. After the histopathological diagnosis, the patient received hospice care, and euthanasia was performed 52 days after the first visit.

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INTRODUCTION

Malignant fibrous histiocytoma is a tumor with histological characteristics resembling histiocytes and fibroblasts (Vail *et al.*, 2019). It is known as a type of soft tissue sarcoma characterized by the presence of variably fibroblastic and less obviously histiocytic cells and variable numbers of non-inflammatory cells (Hasegawa *et al.*, 2003; Kim *et al.*, 2018, 2021). The term 'fibrohistiocytic' was judged to be a misnomer based on electron microscopy and immunohistochemical analysis, and was revised in 2002 in the World Health Organization (WHO) of soft tissue tumors and named undifferentiated pleomorphic sarcoma (Vail *et al.*, 2019). The tumor has been reported in various animals, including humans, dogs and horses (Biervliet *et al.*, 2004; Seomangal *et al.*, 2019; Vail *et al.*, 2019). Although pleomorphic sarcomas are the most common type of soft tissue sarcoma in humans, few have been reported in veterinary medicine, with a reported incidence of only 0.34% of all dog tumors (Waters *et al.*, 1994; Kim *et al.*, 2018, 2021; Vail *et al.*, 2019). Pleomorphic sarcomas are malignant and invade surrounding tissues with distant metastasis to several sites with various clinical symptoms depending on the location of the tumor (Waters *et al.*, 1994; Kim *et al.*, 2018, 2021; Vail *et al.*, 2019).

This case report describes hepatic pleomorphic sarcoma with metastasis to the lungs and thoracic and abdominal lymph nodes in a dog.

History: A 3.5-year-old neutered female, Alaskan Malamute, dog presented to our hospital with a primary complaint of severe recurrent vomiting and rapid weight loss which had progressively worsened over one week. The patient usually vomited one or two hours after a meal. Blood tests conducted at a local animal hospital showed elevated white blood cell (WBC) counts and C-reactive protein (CRP) values. The patient was prescribed a 3 days course of antibiotics and anti-inflammatory drugs, however, symptoms worsened and the patient was referred to our clinic.

Clinical examination and diagnosis: At presentation to our hospital, the patient weighed 25.7kg and had no abnormalities on physical examination. Blood tests showed that the CRP level had decreased from 95mg/L to 40mg/L, while WBC count had decreased from 35.00×10^9/L to 17.38×10^9/L compared to 3 days prior. All other blood tests values were normal.

Chest radiographs showed signs of stagnant gas in the thoracic esophagus, however, no foreign body was observed. Abdominal ultrasonography showed a mass in the liver and other organs were unremarkable. The solitary

liver mass was located on the left lobe, measured approximately 5cm long and showed a hyperechoic shadow inside the hypoechoic center. The lymph node near the liver was enlarged, due to either neoplastic or reactive changes. It was difficult to clearly determine the location of the mass and evaluate impact on surrounding organs since the patient was large and had a deep abdomen.

Fine needle aspiration of the liver mass was conducted under ultrasound guidance. The FNA slides showed poorly differentiated large round cells with basophilic cytoplasm and ovoid-to-bean shaped nuclei with a few multi-nucleated cells. Additionally, mitotic figures and moderate pleomorphism were also frequently observed (Fig. 1).

The next day, a higher-level examination was performed under general anesthesia to identify the cause of the vomiting and evaluate the mass. Endoscopy confirmed that the mucous membranes of the esophagus, stomach, and anterior part of the small intestine were in good condition. No foreign objects were observed. However, although the patient had fasted for >12 hours and gastric motility seemed good, a significant amount of food was still observed in the patient stomach and in the front of the small intestine. CT revealed a single mass (45.5 × 51.6 × 48.8mm) in the left medial lobe of the liver. In addition, a round nodule measuring 4.4 × 7.9 × 6.4mm was observed in the spleen, with suspected lung and intrathoracic and intraperitoneal lymph node metastasis. It was then confirmed that the hepatic lymph nodes, which were severely enlarged, were exerting some pressure on the gastric pylorus (Fig. 2).

A FNA confirmed metastasis in the sternal lymph node nine days after initial presentation. A surgical biopsy was performed for histological examination of the liver mass to confirm the diagnosis and evaluate the malignancy of the tumor (Fig. 3A). The cut-surface of the mass was heterogeneously red-to-yellowish (Fig. 3A). with a firm-to-elastic consistency. This biopsy sample was fixed in 10% neutral buffered formalin overnight and routinely processed. This processed tissue was embedded in paraffin and then cut into 3–4µm thick sections. Microscopy of the biopsy samples showed multinucleated giant histiocytoid cells with round-to-spindle shapes, oval nuclei, and abundant eosinophilic cytoplasm (Fig. 3B). These neoplastic cells showed high cellularity, prominent nuclei and nucleoli with marked atypia and moderate cellular pleomorphism. Mitotic figures were also frequently observed in these histiocytoid cells, suggesting malignancy (Fig. 3B). These neoplastic cells were arranged in clusters and were separated by fibroblastic-like cells with fusiform and spindle shapes arranged in cartwheel and interwoven patterns (Fig. 3B). Due to poor differentiation of the neoplastic cells, immunohistochemistry staining was performed for the differential diagnosis, which included sarcomas such as rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, and histiocytic sarcoma. Immunohistochemistry staining against Desmin (a marker for myogenic differentiation), Vimentin (a marker for mesenchymal origin cells), and Iba-1 (a marker for histiocytes) was performed (Fig. 3C-E). The absence of detectable Desmin reactivity excluded muscle originated neoplasms such leiomyosarcoma and rhabdomyosarcoma (Fig. 3C). Positive reactivity against Vimentin suggested that these neoplastic cells were of mesenchymal origin (Fig. 3D). The neoplastic cells also showed strong positive reactivity against Iba-1, which is a marker for monocytic and histiocytic origin (Fig. 3E). Considering the proliferation of fibroblast-like cells shown on H&E staining, Masson's Trichrome and α-SMA immunohistochemistry staining were further performed (Fig. 3F). Masson's Trichrome staining further confirmed the massive proliferation of fibroblasts, and α-SMA showed that these fibroblasts were of myofibroblast origin (Fig. 3F). Based on the H&E and other special stains, the patient in the present case was diagnosed with malignant fibrous storiform-pleomorphic histiocytic sarcoma.

Differential diagnosis: In this study, the dog was presented to our hospital with a history of severe vomiting and rapid weight loss. Based on the main symptoms, the differential diagnoses of the patient were classified into systemic problems, gastrointestinal conditions and intra-abdominal but non-gastrointestinal conditions. First, systemic problems such as metabolic or endocrine disease were excluded because there were no abnormalities other than evaluated inflammation values in the history, physical examination and blood tests. On diagnostic tests, we confirmed a suspected primary hepatic mass and some metastatic findings, such as enlarged lymph nodes and pulmonary nodules. Additionally, on a CT scan, severely enlarged hepatic lymph nodes were pressing the gastric pylorus. Histological examination of the incisional biopsy from a liver mass revealed an atypical spindle cell proliferation consistent with a spindle cell tumor. Possible differentials of hepatic tumors could include a poorly differentiated sarcoma of soft tissue origin, a histiocytic sarcoma and a spindle cell-type carcinoma. The hepatic tumor was diagnosed as undifferentiated hepatic pleomorphic sarcoma using immunohistochemistry staining and the sternal lymph node FNA also showed similar cell patterns to the hepatic tumor, thus confirming the progression of the metastasis.

Treatment adopted: Because the disease had already metastasized throughout the body, hospice treatment was started after consulting with the owner. As a hospice treatment, periodic imaging tests were used to estimate the progress of the tumor and a soft diet was fed in small volumes and frequently to prevent vomiting. Symptomatic treatment was performed if clinical symptoms worsened or newly appeared.

After that, the dog did not show any symptoms other than intermittent vomiting for a month, but she visited the hospital due to a sudden deterioration in her condition. On thoracic radiograph, a pleural effusion was confirmed, and a total of 1.2L of exudate fluid was punctured. In cytology of fluid, there were no suspicious tumor cells other than erythrocytes and a few neutrophils. The dog was rechecked by ultrasound, and the liver mass, multiple intraperitoneal lymph nodes (including liver lymph nodes), and intrathoracic lymph nodes were all enlarged. In addition to the existing mass, three new nodules in the liver, overall degeneration of the spleen parenchyma, and a nodule in the pancreas were confirmed.

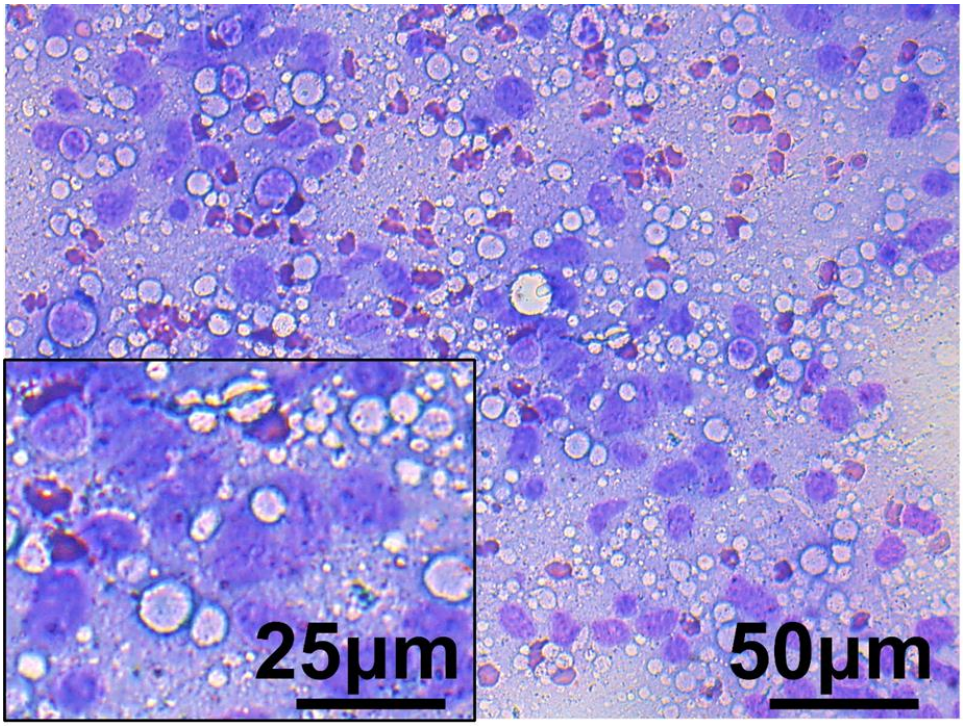

Fig. 1: A representative image of FNA slide. The samples were composed of aggregates of large round cells characterized by basophilic cytoplasm, and ovoid-to-bean shaped nuclei. Occasional mitotic figures and moderate pleomorphism were observed. Scale bar = 50µm, Inset = 25µm.

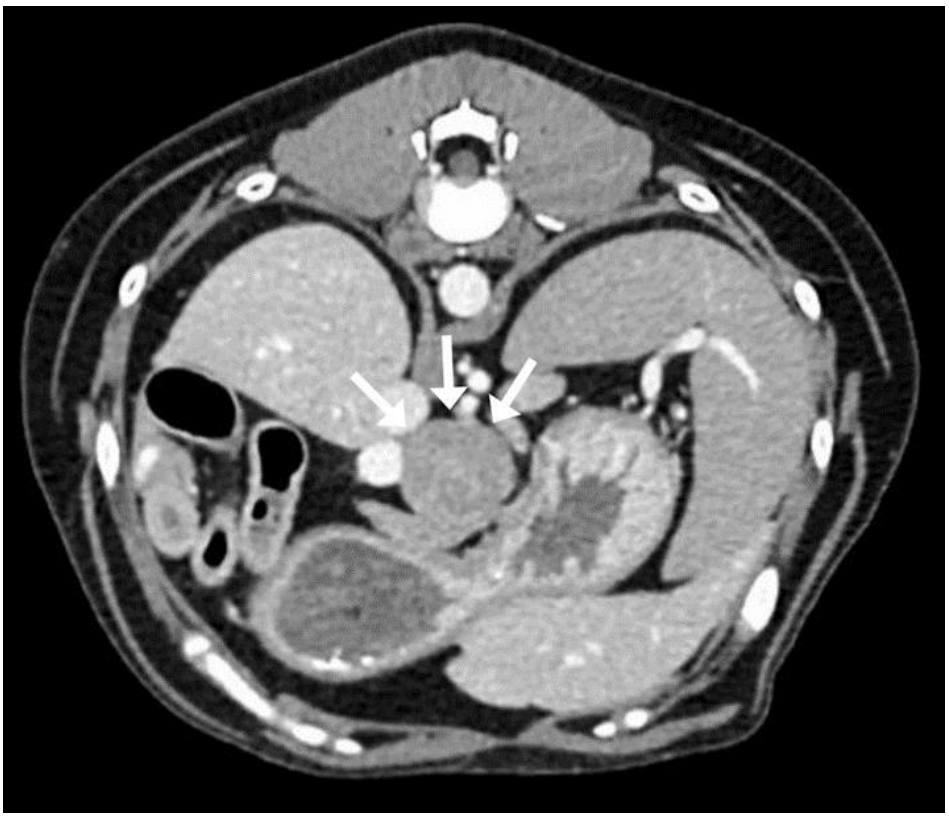

Fig. 2: Computed tomography of the abdomen. The hepatic lymph nodes, which were very enlarged, exerted some pressure on the gastric pylorus (arrows).

Two days later, the patient's condition was greatly reduced. Because of severe vomiting, neither drinking water nor feeding was possible. After hospice care with fluid therapy for several days, euthanasia was performed 52 days after the first visit.

DISCUSSION

Primary liver tumors themselves are uncommon, accounting for less than 1.5% of all tumor cases in dogs, of which 77% were reported as hepatocellular carcinoma. Among solitary liver tumors, pleomorphic sarcomas are rarely diagnosed in both of humans and animals (Mass and Talmon, 2018; Vail *et al.*, 2019).

Although no standard treatment guidelines exist for pleomorphic sarcomas, surgical management is known as the main treatment (Kim *et al.*, 2018; Vail *et al.*, 2019). However, in almost patient, local recurrence after surgery or distant metastases occurred, therefore, the prognosis for advanced pleomorphic sarcomas is very poor, even with combined and multimodal therapy (Waters *et al.*, 1994; Vail *et al.*, 2019; Kim *et al.*, 2021).

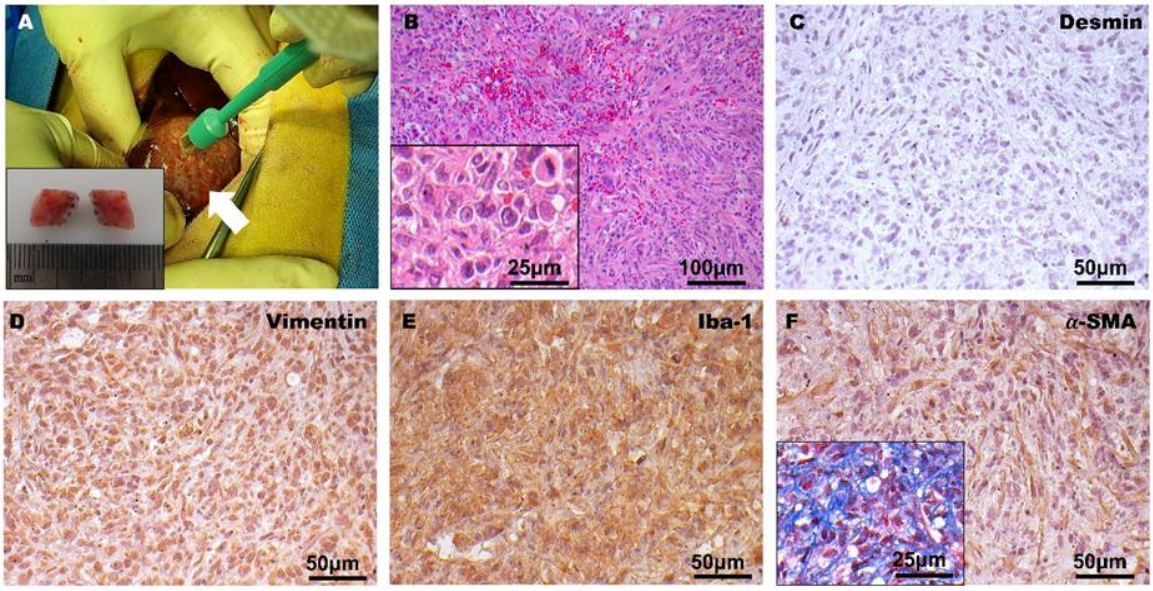

Fig. 3: Representative gross and histopathological images of the biopsy sample. (A) The gross image of the biopsy. The cut-surface of the mass was heterogeneously red-to-yellowish with firm-to-elastic texture. (B) The representative H&E, (C) Desmin, (D) Vimentin, (E) Iba-1, and (F) α -SMA and Masson's Trichrome image. The mass was mainly composed of histiocytoid neoplastic cells with oval and bean shaped nuclei and abundant eosinophilic cytoplasm with high cellularity and moderate pleomorphism indicating their malignancy. These neoplastic cells were negative against Desmin, but positive against Vimentin, Iba-1, α-SMA and Masson's Trichrome staining showing their histiocytic and myofibroblast origin. Scale bar = 50µm, Inset = 25µm.

In addition, as with pleomorphic sarcomas, fine needle aspiration alone cannot make an accurate diagnosis and often does not provide information about the tumor, so a biopsy should always be considered (Vail *et al.*, 2019). Depending on the type of tumor, the patient's prognosis can vary. Thus, differential diagnosis of the sarcomas including leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma and histiocytic sarcoma, histopathological examination with special staining is necessary. In our study, the patient diagnosed with undifferentiated pleomorphic sarcoma based on immunohistochemistry staining and we could be explaining a poor prognosis to owner.

Pleomorphic sarcomas can metastasize to various organs, such as the lungs, lymph nodes, liver, and spleen, and show various clinical symptoms depending on the affected location (Waters *et al.*, 1994; Vail *et al.*, 2019; Kim *et al.*, 2018, 2021). In this study, the patient visited the hospital with repeated vomiting, but there were no specific findings other than fluctuations in inflammation levels in the initial blood tests, and no clear correlation between the liver mass and gastrointestinal symptoms was confirmed in radiographic and ultrasound examinations. However, higher-level examinations, such as CT, confirmed that vomiting was induced by physical obstruction of the gastrointestinal tract caused by hypertrophy due to neoplastic changes in the lymph nodes. Clinical symptoms can also be caused by metastatic lesions other than the primary tumor, so if a clear correlation between clinical symptoms and mass is not found, higher-level examinations should be considered.

Clinically, this patient did not show any symptoms other than vomiting, but after 2 months, the condition worsened, with difficulty breathing, loss of appetite, lethargy, and pain. Because pleomorphic sarcomas metastasize to various sites and progress very aggressively, various clinical symptoms may appear quickly, so careful monitoring is required. Treatment methods are limited for this tumor and the prognosis is very poor in the case of systemic metastasis. Thus, it is better to detect and diagnose as early as possible with higher level examination.

Author contributions: All authors made the diagnosis and had direct patient contact. JY was main clinician and wrote the manuscript. YS and M performed the surgery for biopsy. SK and KJ carried out the diagnosis using radiography, ultrasound and CT scan. JK carried out the histopathological diagnosis and SG supervised this study.

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