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Peritoneal fibrosarcomatous mesothelioma in a cat

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Abstract. Primary tumors of serosal surfaces are uncommon in veterinary medicine. Mesothelial neoplasms can be benign or malignant, and are classified as predominantly epitheloid, mixed (biphasic), or fibrous (spindle cell, fibrosarcomatous), with fibrous mesotheliomas reported least in domestic species. A 9-year-old Domestic Shorthair cat presented on emergency with a brief history of weakness and lethargy. On presentation, the cat was semicomatose, hypothermic, and hypotensive with a markedly distended abdomen. Approximately 1 liter of serosanguineous fluid was removed via abdominocentesis. Diagnostic imaging and cytologic evaluation of fine-needle aspirates were suggestive of neoplasia, and the cat was subsequently euthanized. At necropsy, the omentum was contracted cranially into an irregular lobular mass that surrounded the stomach and proximal intestinal tract, and focally infiltrated the spleen. Both visceral and parietal peritoneal surfaces were thickened and contained off-white friable material and occasionally firm fibrous plaques. Microscopically, serosal surfaces were expanded by neoplastic spindle cells, which were often accompanied by moderate to abundant fibrous stroma. Neoplastic cells had varying degrees of immunoreactivity for cytokeratin, vimentin, desmin, and smooth muscle actin, which was consistent with the diagnosis of mesothelioma.

Key words: Abdominal cavity; cancer; cats; feline; fibrosarcomatous; mesothelioma.

A 4.5-kg female spayed Domestic Shorthair cat presented to the Iowa State University Emergency Service (Ames, Iowa) with a 1-day history of anorexia, adipsia, weakness, and lethargy. The patient was not current on rabies or feline viral rhinotracheitis, calicivirus, and panleukopenia vaccinations and was housed outdoor and indoor. The owners noted the cat was severely ataxic the evening prior to presentation, and that she had vomited the morning of presentation.

On presentation, the patient was semicomatose. Physical examination revealed severe hypothermia (34.3°C), bradycardia (137 beats/min), and eupnea (16 breaths/min). She was 10–12% dehydrated and severely hypotensive, with a systolic blood pressure of 50 mmHg and weak, thready femoral pulses. The abdomen was severely distended and symmetrically enlarged.

An abdominocentesis was performed, and 1,030 ml of serosanguineous fluid was removed. Fluid analysis revealed glucose of 307 mg/dl, lactate of 9.1 mmol/l, and specific gravity of 1.028. Initial blood work demonstrated a glucose of 244 mg/dl (reference [ref.] interval: 70–135 mg/dl), lactate of 1.7 mmol/l (ref. interval: <2.5 mmol/l), packed cell volume of 40% (ref. interval: 30–45%), total solids of 7.2 g/dl (ref. interval: 6.1-8.0 g/dl), and blood urea nitrogen (BUN) reagent strip[a] of 50–80 mg/dl (ref. interval: 5–15 mg/dl). After fluid therapy, additional blood was drawn for a complete blood cell count (CBC), serum biochemistry, *Feline leukemia virus* (FeLV) antigen testing,[b] and *Feline immunodeficiency virus* (FIV) antibody testing.[b] The CBC demonstrated leukopenia of 3.74 (ref. interval: 5.5–19.5 × 10^3/μl), hematocrit of 29.9% (ref. interval: 30–45%), lymphopenia of 0.15 (ref. interval: 1.5–7.0 × 10^3/μl), and red blood cell distribution width of 13.4% (ref. interval: 15–22%). Serum biochemistry showed hyponatremia of 127 mEq/l (ref. interval: 155–165 mEq/l), hypochloremia of 93 mEq/l (ref. interval: 123–131 mEq/l), hypocalcemia of 6.0 mg/dl (ref. interval: 8.5–11.2 mg/dl), hypermagnesemia of 6.15 mg/dl (ref. interval: 1.95–3.04 mg/dl), azotemia (elevated BUN) of 102.9 mg/dl (ref. interval: 15–35 mg/dl), hyperglycemia of 243 mg/dl (ref. interval: 70–135 mg/dl), hypoproteinemia of 4.6 g/dl (ref. interval: 6.1–8.0 g/dl), and increased anion gap of 18 (ref. interval: 12–16). Enzyme-linked immunosorbent assay testing for FeLV and FIV were negative.

The patient was stabilized, and abdominal radiographs were taken, which demonstrated a moderate decrease in serosal demarcation throughout the peritoneal space. This was most prominent within the middle, ventral aspect of the abdomen. Also, there was a mottled soft tissue and/or fluid

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Figure 1. Mesothelioma of the peritoneum; cat. The omentum is contracted cranially into a multinodular mass (arrows). Multifocal fibrous plaques can be seen on the reflected abdominal wall (asterisks), and there is a small amount of serosanguineous fluid in the peritoneal cavity.

and gas opacity extending cranially from the middle, ventral abdomen. Remaining intra-abdominal structures were unable to be assessed due to border effacement of their margins. Abdominal ultrasonography revealed free fluid throughout the abdomen, and a markedly nodular, and hyperechoic omental curtain. In certain regions, the omentum was heterogenous with less echoic central tissue surrounded by more hyperechoic areas. Radiographic conclusions were possible carcinomatosis or sarcomatosis. Other considerations included infectious or inflammatory diseases such as feline infectious peritonitis or fungal infection.

Transabdominal fine-needle aspirates were taken of the irregularly thickened omentum at 3 sites and submitted for cytology. Large, atypical, rounded cells with fine vacuoles were noted in all cytology samples. Single, bi-, and multinucleated cells were observed with a large variability and irregularly shaped nucleoli. These cells could not be differentiated from macrophages, endothelial or epithelial cells. Differential diagnoses included neoplasia and granulomatous inflammation. Possible neoplasms included adenocarcinoma, mesothelioma, or hemangiosarcoma.

Due to poor prognosis, the cat was euthanized, and a necropsy was performed. On gross examination, the omentum was

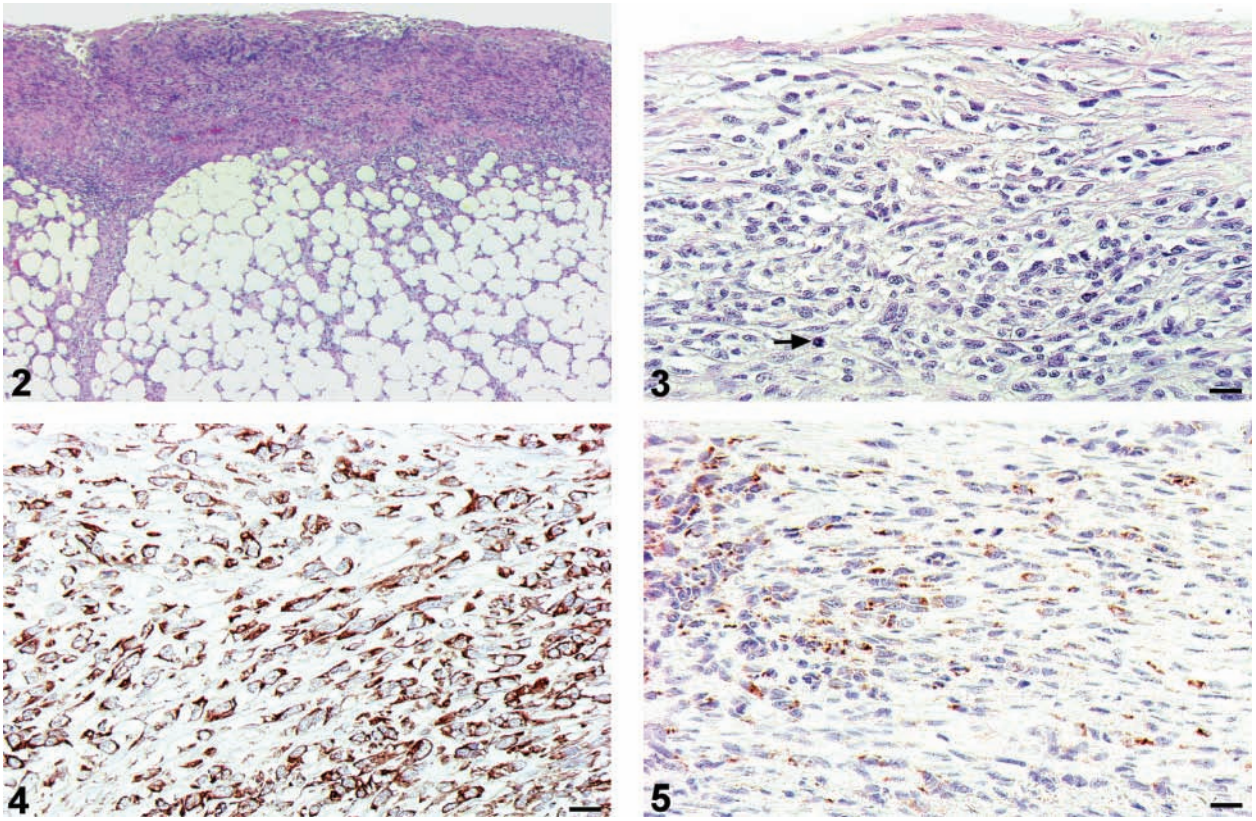

Figure 2. Omentum; cat. Peritoneal fibrosarcomatous mesothelioma characterized by marked expansion of the peritoneum by neoplastic spindled cells and moderate to abundant fibrous connective tissue. Bands of neoplastic cells multifocally extend into underlying adipose tissue. Hematoxylin and eosin. **Figure 3.** Omentum; cat. Higher magnification of neoplastic mesenchymal cells in Figure 2. Neoplastic cells are arranged in streams with moderate fibrous connective tissue stroma. A mitotic figure (arrow) is present. Hematoxylin and eosin. Bar = 20 μm. **Figure 4.** Peritoneal fibrosarcomatous mesothelioma; cat. The vast majority of neoplastic cells exhibited strong cytoplasmic immunoreactivity for vimentin. Bar = 20 μm. **Figure 5.** Peritoneal fibrosarcomatous mesothelioma; cat. Fewer neoplastic cells exhibited moderate cytoplasmic immunoreactivity for cytokeratin. Bar = 20 μm.

contracted cranially forming a large, irregular, firm, tan, multinodular mass that was approximately 10 cm in diameter (Fig. 1). The mass surrounded the intestinal tract, including the stomach, and was attached to the spleen. The spleen was apparently focally infiltrated by the mass, and the capsular surface was diffusely covered by off-white semifriable material. The peritoneal cavity contained about 30 ml of serosanguineous fluid, and the parietal peritoneum was diffusely thickened with multifocal, firm, white to tan plaques ranging from 2 to 6 cm in size. The liver was diffusely pale yellow in color, with a focal accumulation of similar off-white material on the capsular surface.

Specimens of multiple tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Sections of omentum were also labeled with monoclonal antibodies against vimentin,[c] cytokeratin,[d] desmin,[e] smooth muscle actin,[f] and S-100.[g] Histologically, the omentum was superficially expanded by an unencapsulated and moderately well-demarcated neoplasm composed of spindled cells (Fig. 2), which occasionally infiltrated deep into residual omental adipose tissue. Neoplastic cells were arranged in streams and bundles, and were supported by moderate to marked amounts of fibrovascular to densely fibrous stroma (Fig. 3). Neoplastic cells had variably distinct cell borders and contained small amounts of fibrillar eosinophilic cytoplasm and round to elongate nuclei with finely stippled chromatin and 1–2 prominent nucleoli. There was moderate anisocytosis and anisokaryosis, and the mitotic rate was high (2–3 per 400× field) with occasional bizarre mitoses. The peritoneum of the abdominal wall was markedly expanded by similar neoplastic cells and abundant fibrous tissue, which occasionally superficially invaded underlying skeletal muscle. The capsular surface of the spleen was lined by similar neoplastic cells and stroma, which focally infiltrated and effaced splenic parenchyma. Neoplastic cells were also present on the peritoneal surfaces of the liver, adrenal glands, stomach, small intestine, and urinary bladder. Neoplastic cells were strongly positive for vimentin (Fig. 4) and moderately positive for cytokeratin (Fig. 5). Additionally, there was weak to moderate labeling for desmin, and strong and relatively widespread labeling for smooth muscle actin. Immunohistochemistry for S-100 was negative. Masson trichrome stain revealed fine fibrils and broad bundles of collagenous stroma supporting and separating neoplastic cells. Prussian blue staining for iron (ferruginous bodies) was negative. Appropriate positive and negative control tissues were included in all labeling procedures.

In consideration of the gross, microscopic, and immunohistochemistry findings, the favored diagnosis in the present case is fibrosarcomatous mesothelioma. Differential diagnoses based on histology were metastatic carcinoma (sarcomatoid) or sarcoma (e.g., intestinal leiomyosarcoma), and liposarcoma. A primary neoplasm was not identified, making metastatic carcinoma or sarcoma less likely. The presence of adipocytes entrapped by the neoplastic spindle cell population, especially within the omentum, prompted the consideration of liposarcoma. However, the histomorphology of the tumor was inconsistent with that generally reported for liposarcoma (sheets of round to polygonal cells, which usually contain diagnostic intracytoplasmic lipid vacuoles), as were the immunohistochemistry results. Liposarcomas are cytokeratin negative and often S-100 positive.[4] Distinguishing features of the neoplasm in the current case include the distribution of neoplastic cells along serosal surfaces and expression of both vimentin and cytokeratin. Additionally, while desmin and smooth muscle actin are not considered discriminatory markers for sarcomatous mesothelioma, their expression pattern as reported herein has been described in human sarcomatous mesotheliomas.[9]

The pericardial, pleural, and peritoneal cavities, internal organs, and tunica vaginalis of the testes are lined by a monolayer of cells termed the mesothelium. The mesothelium functions to provide protection from physical damage and invading pathogens. In addition, this nonadhesive layer plays a major role in fluid and cell transportation, surfactant secretion, tumor cell adhesion, antigen presentation, inflammation, and tissue repair.[11,16] These mesenchymal derivatives differentiate from a rounded or cuboidal form to an elongated, flattened, squamous shape.[10] Cuboidal cells may still be observed during an activated or increased metabolic state (e.g., peritonitis) and are typically located in sampling grounds such as lymphatic lacunae or "milky spots" on the omentum.[11,16] Mesothelial cells regenerate from multipotent precursor cells located in the submesothelium,[11] and typically express both mesenchymal and epithelial intermediate filaments (vimentin and desmin, and cytokeratins, respectively) permitting a phenotypic duality. It is expression of these markers that allows differentiation of malignant mesothelial disease from other malignant processes, such as carcinomatosis.

Three primary histologic patterns of mesothelioma are described: epithelioid, sarcomatoid (spindle cell, fibrous, fibrosarcomatous), and mixed (biphasic).[7] Malignant mesotheliomas (MM) are rare in all species, but occur most rarely in cats. Felines usually present with spontaneous and idiopathic forms in adulthood.[2] Malignant mesothelioma has been associated with many suggested predisposing factors such as past radiation exposure, chemical exposure, genetic predisposition, and asbestos and non-asbestos fibers.[15]

Malignant mesothelioma is essentially a diagnosis of exclusion and is based on integration of history, clinical findings, imaging, and morphologic studies such as gross pathology, histology, immunohistochemistry, and electron microscopy. Effusions are a common clinical finding due to exudation from obstructed lymphatics and tumor surfaces.[15] Advanced imaging such as abdominal ultrasound is usually not helpful except late in the disease process. Computed tomography has been used to show pulmonary nodules associated with thoracic effusion, but also has limited value.[15]

Cytology is typically nondiagnostic in itself even though malignant mesothelial cells will exfoliate into effusions. The challenge in diagnosing MM with cytology lies in discerning reactive hypertrophic mesothelial cells from malignant cells due to overlapping cytologic features.[15] A recent human study used logistic regression analysis to determine differentiating cytologic features that can distinguish between reactive mesothelial proliferation, adenocarcinoma, and MM cells in effusion samples.[3] Ultimately, 3 cytologic features were determined to distinguish MM from adenocarcinoma: giant atypical mesothelial cells, acinar structures, and nuclear pleomorphism with the latter two being characteristics of adenocarcinoma. In addition, 3 features were determined to distinguish MM from benign (reactive) mesothelial proliferation: cell ball formation, cell-in-cell engulfment, and monolayer cell aggregates with the latter being characteristic for benign mesothelial proliferation. Even with these criteria and adequate cytologic samples, a definitive diagnosis was made in only approximately 66% of cases.[3]

Typical postmortem findings of MM in domestic animals include multiple sessile or pedunculated nodules ranging in size from a few millimeters to >5 cm in diameter, or villous projections, arising from a thickened mesentery or serosal surface. Masses may eventually coalesce to encase organs in tumor tissue, as with the omentum in the current case. Prior reports of peritoneal mesothelioma in cats describe a gross presentation of multiple nodules associated with serosal surfaces.[1,2,8,12] In the case reported herein, the gross presentation of a contracted omental mass accompanied by a thickened peritoneum with fibrous plaques is unique, and likely attributable to the distinct morphology of the tumor. Additionally, feline peritoneal mesotheliomas reported to date have been characterized histologically as epithelioid or biphasic, not fibrous or fibrosarcomatous.

Mesotheliomas in domestic species were once thought to rarely metastasize and to have limited invasive growth. A recent study examining both pleural and peritoneal mesotheliomas in the cat reported metastasis in 6 of 10 cases reviewed.[2]

Definitive diagnosis of MM via histology can be challenging. Depending on the morphology of the neoplasm, common differential diagnoses for mesothelioma include carcinoma or adenocarcinoma, reactive mesothelial cell proliferation, metastatic squamous cell carcinoma, fibrosarcoma, malignant fibrous histiocytoma, and reactive cellular fibrosis. In veterinary medicine, common secondary histologic patterns of epithelioid mesothelioma include papillary, tubular, tubulopapillary, and solid.[6] Fibrous or fibrosarcomatous forms of mesothelioma, the least common form in animals, consist of predominantly spindle-shaped cells supported by a fibrous connective tissue stroma, as in the present case. Biphasic mesotheliomas contain both epithelioid and spindle-shaped cells, and are relatively rare with regard to peritoneal mesotheliomas. This is important, as biphasic patterns are less amenable to treatment and carry a grave prognosis compared to other forms.[7]

Immunohistochemical staining is useful in ruling out other diseases, but currently there are no cellular markers specific for mesothelial cells. Instead, immunohistochemistry is based on panels of positive (commonly present) and negative (commonly absent) markers for mesothelioma.[14] In cats, 1 study determined vimentin and broad spectrum cytokeratin (CK) expression to be a constant feature of all mesotheliomas, whether epithelial or spindle-cell type.[2] This study also concluded that a secondary antibody panel containing HBME-1 (a monoclonal antibody that recognizes an uncharacterized antigen on mesothelial microvilli), e-cadherin, carcinoembryonic, CK5/6, and CKAE1/AE3 markers are potentially valuable in further differentiating feline fibrosarcomatous mesothelioma from other forms. Neoplastic cells in the tumor reported herein were strongly positive for vimentin and intermediately positive for cytokeratin.

Ultrastructural features are thought to be useful only for diagnosing well-differentiated epithelial mesotheliomas as opposed to fibrosarcomatous mesotheliomas.[5] Characteristic electron microscopy findings include long, slender microvilli present on all surfaces, perinuclear tonofilaments, and desmosomes. In addition, 1 case of peritoneal mesothelioma in a cat demonstrated psammoma bodies via electron microscopy.[1] Electron microscopy was not performed in the current case. New diagnostics are on the horizon and include microarray studies using gene expression ratio techniques to both confirm diagnosis and prognostication.[15]

Treatments available may include intracavitary and/or systemic chemotherapeutics, such as carboplatin and doxorubicin or mitoxantrone, respectively. Radical resection, radiation, and clinical supportive care are additional therapies.[13] In fact, intracavitary carboplatin and piroxicam have been shown to decrease effusion production in the case of one cat.[13] Palliative therapies in nonsurgical human patients may include vinorelbine (single agent chemotherapy) and pemetrexed (a multi-targeted antifolate) combined with cisplatin. Numerous cytokines (e.g., IL-2, alph-2b) have been proven to be beneficial in human bulky disease. Most recently, growth factor receptor inhibitors (e.g., bevacizumab, gefitinib) are under investigation.[15] Median survival times have not been officially reported due to the low rate of occurrence of the disease and because most animals are euthanized at the time of diagnosis.[15]

In conclusion, a case of peritoneal fibrosarcomatous mesothelioma in a cat is presented in the current report. Malignant mesothelioma is a rare yet highly lethal neoplasia that is complex and difficult to diagnose. Although many diagnostic tools and experimental treatments have been implemented in human trials, veterinary medicine is in need of species-specific information. The present report adds to the veterinary literature regarding mesothelioma in animal species, and serves to evaluate feline mesotheliomas to better enhance diagnostics, prognostication, and therapeutics.

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Sources and manufacturers

a. Azostix, Siemens Healthcare Diagnostics Inc., Tarrytown, NY.
b. SNAP FIV/FeLV, IDEXX Laboratories Inc., Westbrook, ME.
c. Mouse anti-vimentin, MNF116, Dako North America Inc., Carpinteria, CA.
d. Mouse anti-human cytokeratin, V9, Dako North America Inc., Carpinteria, CA.
e. Mouse anti-desmin, Dako North America Inc., Carpinteria, CA.
f. Mouse anti-smooth muscle actin, BioGenex Laboratories Inc., San Ramon, CA.
g. Rabbit anti-S-100, Dako North America Inc., Carpinteria, CA.

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