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Brief Communication

Journal of Veterinary Diagnostic Investigation
2019, Vol. 31(6) 879–882
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DOI: 10.1177/1040638719879737
jvdi.sagepub.com

Inflammatory myofibroblastic tumor of the pancreas in a dog

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Abstract. A large, ill-defined, firm, multinodular mass involving the pancreas was confirmed on postmortem examination of a 5-y-old, male Rottweiler that died following acute respiratory distress syndrome, after a period of anorexia and lethargy. Histologically, the mass consisted of plump spindle cells admixed with a variable number of macrophages, lymphocytes, plasma cells, and neutrophils. Foci of coagulative necrosis and hemorrhage were also observed. Spindle cells strongly reacted to antibodies against vimentin, α–smooth muscle actin, and calponin, whereas desmin was expressed only mildly and focally. Pan-cytokeratin, KIT, glial fibrillary acidic protein, and S100 protein were nonreactive. Variable numbers of MAC 387–positive cells, CD3+ lymphocytes, and numerous blood vessels were also detected throughout the mass. Histologic and IHC findings were consistent with a diagnosis of inflammatory myofibroblastic tumor of the pancreas.

Key words: dogs; inflammatory myofibroblastic tumor; pancreas; pancreatitis.

Inflammatory myofibroblastic tumor (IMT), previously known as inflammatory pseudotumor, is a rare condition of unknown etiology, composed of spindle-shaped myofibroblasts or fibroblasts accompanied by an inflammatory infiltrate of variable proportions of lymphocytes, plasma cells, histiocytes, with occasional admixed eosinophils and neutrophils.[9,11] Although previously considered to be an inflammatory lesion following trauma, surgery, or infection,[4,8,16] the 2013 World Health Organization classification for this rare tumor in humans classified IMT as a distinctive neoplasm of intermediate biologic potential, given a tendency for local recurrence and a small risk of distant metastasis.[6,7] In human patients, IMT occurs primarily in visceral and soft tissues of children and young adults, especially in the first 2 decades of life, and the most common localizations have been reported in lung, mesentery, and omentum.[3] A localization of IMT in the human pancreas is very rare and needs to be differentiated from pancreatic enlargement as a result of chronic pancreatitis or pancreatic cancer,[12,14] given that gross appearance may be similar. IMT has been described occasionally in dogs in various anatomic sites (Table 1),[1,8,11,13,16,17] although localization in the pancreas has not been reported previously in the veterinary literature, to our knowledge.

A 5-y-old, male Rottweiler was presented with a 4-d history of anorexia and lethargy. On physical examination, the dog appeared depressed and 10% dehydrated, although it was in good body condition (score = 5 of 9). Respiratory rate was 45/min, heart rate 120/min, and rectal temperature 38.5°C. The femoral pulse was weak, and abnormal breathing sounds were recorded on thoracic auscultation. Abdominal palpation revealed a tense and firm abdomen, with the presence of abdominal pain, and a large mass in the epigastric area. A complete blood count revealed mild leukocytosis (15.0×10^9/L; reference interval [RI]: $5.2–13.9 \times 10^9$/L) with 1% band neutrophils. The serum biochemical profile showed increased total bilirubin (11.1 µmol/L; RI: 1.7–5.1 µmol/L), alanine aminotransferase (96 U/L; RI: 15–55 U/L), aspartate aminotransferase (144 U/L; RI: 15–40 U/L), *alkaline phosphatase* (1,250 U/L; RI: 42–180 U/L), *urea* (40.7 mmol/L; RI: 6.4–19.6 mmol/L), cholesterol (16.2 mmol/L; RI: 2.8–8.6 mmol/L), triglyceride (2.6 mmol/L; RI: 0.3–1.4 mmol/L), glucose (7.8 mmol/L; RI: 3.3–6.1 mmol/L), lipase activity (2,280 U/L; RI: 0–560 U/L), and C-reactive protein (889 nmol/L; RI: 0–95 nmol/L). Serum specific canine pancreatic lipase (Spec cPL) was 560 µg/L (RI: 0–200 µg/L).

Abdominal ultrasound examination revealed a heterogeneous mass involving the pancreas, surrounded by poorly defined tissue with mixed echogenicity (Fig. 1). Systemic inflammatory response syndrome (SIRS) secondary to acute pancreatitis and/or pancreatic neoplasia was diagnosed based on history and clinical findings. Despite supportive treatment, the dog died of acute respiratory distress syndrome (ARDS). Autopsy confirmed the

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Table 1. Case reports of canine inflammatory myofibroblastic tumor displaying breed, sex, age at the time of diagnosis, and tumor localization.

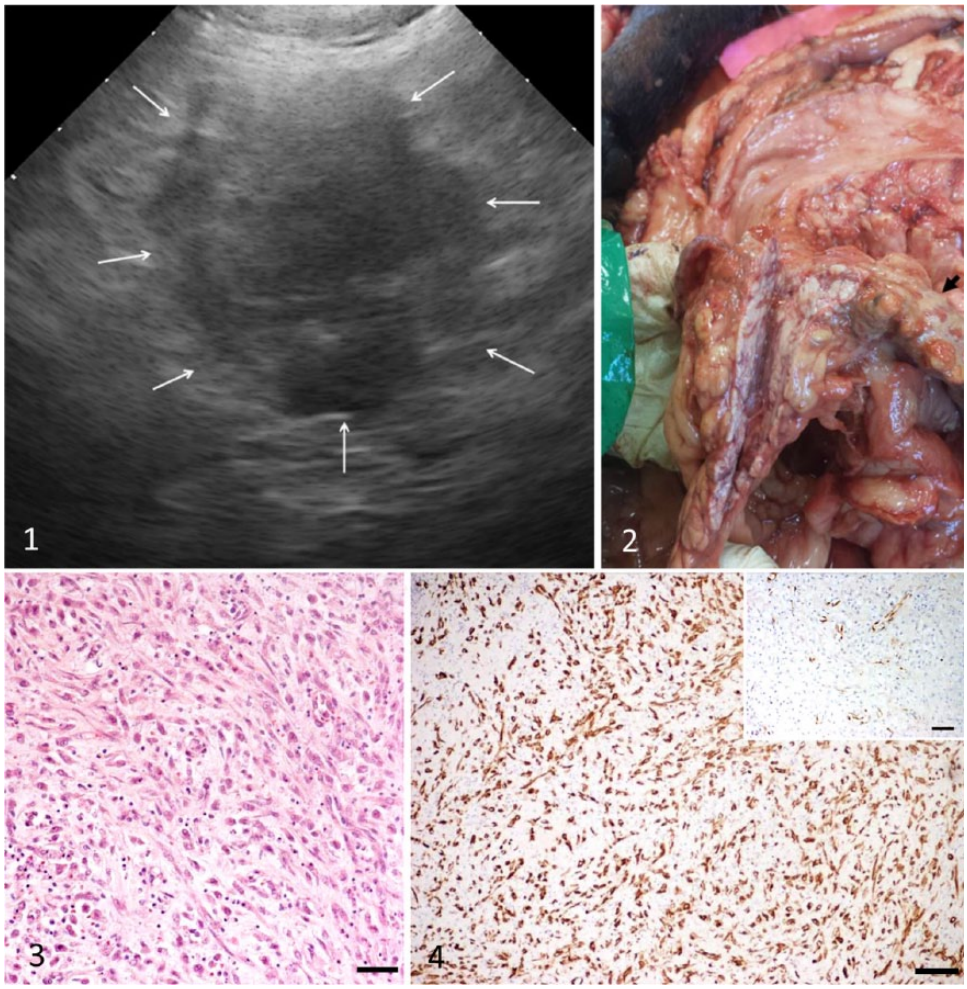
Breed	Sex	Age (y)	Localization	References
Cocker Spaniel	F	13	Urinary bladder	[1]
German Shepherd	M	9	Mitral valve	[17]
Keeshond	CM	9	Subcutis (thigh)	[11]
Leonberger	SF	4.5	Nasal cavity	[16]
Maltese	F	NA	Urinary bladder	[1]
	SF	4	Urinary bladder	[1]
	M	5	Meningeal	[13]
Mixed breed	F	14	Urinary bladder	[1]
	F	12	Spleen	[8]
	CM	11	Retrobulbar	[11]
Poodle	F	9	Urinary bladder	[1]
Shih Tzu	F	7	Urinary bladder	[1]
Terrier	F	13	Urinary bladder	[1]
NA	M	NA	Urinary bladder	[1]

CM = castrated male; F = female; M = male; NA = not available; SF = spayed female.

presence of an ~20 ×13 × 9 cm, ill-defined, firm, multinodular white or gray-yellow to pink mass involving the pancreatic body, with partial extension to the left lobe, and widely (~90%) occupying the lesser omentum (Fig. 2). The surface of the mass had multiple areas of peripancreatic fat necrosis with diffuse inflammation; the cut section was characterized by a mixture of necrotic, hemorrhagic, and/or edematous areas. The mass adhered slightly to the adjacent serosal surface of the liver, partially surrounded the caudal vena cava, and caused moderate compression of the prepyloric region of the stomach. The remaining portions of the pancreas, including part of the left and right lobes, appeared grossly normal to moderately fibrotic. Acute, severe, bilateral, and diffuse interstitial lung disease, associated with the presence of necrotic and hemorrhagic areas, was also observed.

Samples of the mass, adjacent pancreas, and all other major organs were fixed in 10% neutral-buffered formalin, processed routinely, and sections stained with hematoxylin and eosin. Additional sections of the mass and adjacent pancreas were also stained with Masson trichrome and subjected to immunohistochemistry (IHC) using primary antibodies directed against pan-cytokeratin (CK; 1 in 100 dilution, AE1⁄AE3, mouse monoclonal; Dako, Glostrup, Denmark), vimentin (1 in 100 dilution, V9, mouse monoclonal; Dako), α–smooth muscle actin (α-SMA; 1 in 400 dilution, 1A4, mouse monoclonal; Dako), desmin (1 in 50 dilution, D33, mouse monoclonal; Dako), calponin (1 in 50 dilution, CALP, mouse monoclonal; Dako), von Willebrand factor (vWF; 1 in 400 dilution, rabbit polyclonal; Dako), glial fibrillary acidic protein (GFAP; 1 in 500 dilution, rabbit polyclonal; Chemicon International, Temecula, CA), S100 protein (1 in 400 dilution, rabbit polyclonal; Dako), KIT (1 in 800 dilution, polyclonal rabbit; Dako), CD3 (1 in 100 dilution, polyclonal rabbit; Dako), and myeloid/histiocyte antigen (1 in 50 dilution, MAC387, mouse monoclonal; Dako). Immune complexes were treated with secondary biotinylated goat anti-mouse or anti-rabbit antibody (1:200 dilution; Vector Laboratories, Burlingame, CA) and subsequently detected using an avidin–biotin complex method (Vectastain ABC kit; Vector Laboratories). Peroxidase activity was detected using 0.1% hydrogen peroxide in 3,3'-diaminobenzidine solution (MilliporeSigma, St. Louis, MO). Sections were counterstained with Mayer hematoxylin (Merck, Darmstadt, Germany).

Histologically, the mass consisted of plump spindle cells haphazardly arranged in dense, interwoven streams, among which were scattered variable numbers of macrophages, lymphocytes, plasma cells, and neutrophils (Fig. 3). Spindle cells had a moderate-to-large amount of eosinophilic cytoplasm, and mildly anisokaryotic, round-to-ovoid nuclei with 1 or 2 nucleoli and scattered mitotic figures. Foci of coagulative necrosis and hemorrhage were also observed within and at the periphery of the mass, also involving the adjacent pancreatic tissue. Spindle cells reacted strongly to antibodies against vimentin, calponin (Supplementary Fig. 1), and α-SMA (Fig. 4), whereas desmin was only mildly to moderately expressed, with predominantly focal distribution (Supplementary Fig. 1). The spindle cells did not react with antibodies against CK, vWF, KIT, GFAP (Supplementary Fig. 1), or S100 protein. Variable numbers of CD3+ lymphocytes and MAC387-positive cells were dispersed among the spindle cells (Supplementary Fig. 2). Numerous vWF-positive cells lining blood vessels were also present throughout the tumor (Fig. 4). The remaining pancreatic tissue was partially displaced by moderate-to-intense periductal and interstitial fibrosis, as confirmed by Masson trichrome stain (Supplementary Fig. 3). Scattered infiltrates of lymphocytes,



Figures 1–4. Inflammatory myofibroblastic tumor of the pancreas in a dog. **Figure 1.** Ultrasound image with a large, heterogeneous mass (arrows) involving the pancreas, with reduced detail of the surrounding mesenteric tissue. **Figure 2.** Large, ill-defined, multinodular mass involving the pancreatic body, with superficial fat necrosis (arrow) and variegated appearance as a result of necrotic areas. **Figure 3.** Haphazardly arranged plump spindle cells with admixed macrophages, lymphocytes, plasma cells, and neutrophils. H&E. Bar = 22 μm. **Figure 4.** Intense and diffuse labeling of spindle cells for α–smooth muscle actin. IHC. Bar = 45 μm. Inset: several von Willebrand factor–positive blood vessels admixed with negative spindle cells are visible. IHC. Bar = 60 μm.

plasma cells, and histiocytes were also admixed, suggestive of chronic pancreatitis. Histologically, acute, severe pulmonary alveolar damage was characterized by diffuse congestion of alveolar septa, alveolar edema, and formation of hyaline membranes. No significant microscopic lesions were observed in the other organs examined.

Gross, histologic, and IHC results suggested a diagnosis of IMT of the pancreas. Clinicopathologic findings were consistent with a final episode of acute pancreatic necrosis, possibly resulting from relapsing, probably subclinical, chronic pancreatic necrosis and inflammation associated with IMT. Although previous episodes of acute pancreatitis were not reported in the patient history, pancreatic necrosis usually smolders continuously and often asymptomatically in dogs.[10] In addition, it is known that, regardless of etiology, acute pancreatic necrosis and inflammation usually progress to SIRS, a syndrome in which pulmonary complications are the most frequent and potentially the most serious, especially ARDS.[2,5]

An unusual case of chronic pancreatitis as a result of recurrent episodes of acute pancreatitis caused by an IMT in the pancreatic head has been described in a human,[14] suggesting tumor development over a long period of time. In humans, a low worldwide incidence (0.04–0.7%) of IMT of the pancreas has been reported,[6] with 60% located in the pancreatic head. Complete surgical excision is the preferred therapeutic option for this tumor.[6,12,14]

Although regarded previously as a reactive lesion, IMT is, to date, considered to be a neoplastic process,[6,7] and its correct diagnosis is essential for establishing proper disease management and treatment. Given its nonspecific signs and imaging findings, definitive diagnosis of IMT is based on

histologic evaluation,[6,15,16] although transendoscopic biopsies or intraoperative frozen sections do not usually provide enough tissue to obtain a conclusive histologic diagnosis.[6,14]

Distinction of IMT from various soft tissue sarcomas and inflammatory processes may also be challenging, although the histologic features of a population of large spindle-shaped myofibroblastic cells with mild atypia, admixed with inflammatory cells and an irregular vascular network, are considered the hallmarks of IMT.[16,17] Diffuse expression of vimentin, associated with variable expression of myofibroblastic markers, especially α-SMA, represents the common IHC features of IMT reported in the human and veterinary literature.[1,6,11,14,16] In our case, the histologic and IHC features, in association with the lack of gastrointestinal involvement, allowed the differentiation from other types of sarcoma, especially leiomyosarcoma and gastrointestinal stromal tumors. Although rare, IMT should be taken into consideration in the differential diagnosis of pancreatic neoplasms in dogs.

Acknowledgments

We thank Dr. M. Baffoni for her technical assistance.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Supplementary material

Supplementary material for this article is available online.

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