Localization of Pancreatic Inflammation and Necrosis in Dogs

Shelley Newman, Jörg Steiner, Kristen Woosley, Linda Barton, Craig Ruaux, and David Williams

Few studies of the prevalence of histologic lesions of the exocrine pancreas in dogs have been reported, and none of them systematically evaluated the localization of these lesions. The purpose of this study was to describe the anatomic localization of pancreatic inflammation, necrosis, and fibrosis in dogs presented for postmortem examination. Seventy-three pancreata from dogs presented for postmortem examination were evaluated and investigated for the presence of supplicative inflammation (SI), pancreatic necrosis (PN), and lymphocytic inflammation (LI). Sections that showed evidence of SI, PN, or LI also were evaluated for pancreatic fibrosis (F). The tendency for a preferred localization for SI, PN, and LI was evaluated by chi-square analysis. A total of 47 pancreata with histologic evidence of pancreatitis (SI, PN, or LI; F alone was not considered evidence of pancreatitis) were identified. Twenty-four (51.1%) had SI, 23 (48.9%) had PN, and 34 (72.3%) had LI. Of the 47 dogs with SI, PN, or LI, 28 (59.6%) had F. The distribution of SI, PN, and LI between the right and the left limb of the pancreas and among the 5 anatomic regions was random, based on a goodness-of-fit test. We conclude that pancreatic inflammation tends to occur in discrete areas within the pancreas rather than diffusely throughout the whole organ. These findings suggest that a single biopsy is insufficient to exclude subclinical pancreatitis and that there is no preferred site for pancreatic biopsy collection unless gross lesions are apparent.

Key words: Canine; Inflammation; Necrosis; Pancreas.

Pancreatitis has been recognized as the most frequent disease process of the exocrine pancreas in the dog.¹ A uniform classification system for pancreatitis in dogs has not been agreed upon. In contrast, a uniform classification system has been developed for pancreatitis in human patients and was last updated during the 1992 Atlanta Symposium on Pancreatitis.² According to this classification system, acute pancreatitis is defined as an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems that does not lead to permanent changes.³ Chronic pancreatitis is defined as a chronic inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems that leads to permanent changes, mainly fibrosis.² This definition does not make any stipulations about the primary cell type that is responsible for the inflammation in either acute or chronic pancreatitis, even though most cases of acute pancreatitis are predominantly supplicative and many cases of chronic pancreatitis are lymphocytic. Although a determination of chronic pancreatitis can be made on the basis of a single biopsy sample that has an abnormally large number of inflammatory cells and fibrosis, final determination of acute pancreatitis would require a second biopsy after the disease process has subsided that reveals no evidence of fibrosis.

Histologic lesions associated with pancreatitis have been described as either small focal areas of necrosis and inflammation or larger confluent areas.¹ Peripancreatic fat necrosis frequently is present and may extend for some distance into the mesenteric and omental fat. Frequently, destruction of pancreatic tissue is insufficient to cause exocrine pancreatic insufficiency, although areas of pancreatic fibrosis sometimes are discovered as an incidental finding during postmortem examination in dogs with normal digestive function.⁴

Acute necrotizing pancreatitis (ANP), the more severe form of acute pancreatitis, is characterized by extensive pancreatic and peripancreatic necrosis, with severe forms progressing to total dissolution of pancreatic parenchyma with accompanying interstitial hemorrhage.⁵ The inflammatory response associated with ANP can develop rapidly and progresses from interstitial fluid accumulation to deposition of fibrin and leukocytes.⁶ As local circulation is further impaired, additional necrosis occurs in pancreatic acinar cells.⁶ ANP can arise from a single inflamed region, multicentric lesions, or massive involvement of the entire gland.⁶ Dogs that survive acute pancreatitis, or those with recurrent bouts of pancreatitis, may develop classical lesions of chronic pancreatitis (ie, lymphocytic inflammation [LI], fibrosis, and atrophy).⁶ Other lesions associated with chronic pancreatitis include parenchymal atrophy, adhesions, and abscess formation.

Few studies of the prevalence of histologic lesions of the exocrine pancreas in dogs have been reported. No studies have systematically evaluated the localization of inflammation, necrosis, and fibrosis.¹ The purpose of the present study was to describe the anatomic localization of pancreatic inflammatory lesions, necrosis, and fibrosis in dogs presented for postmortem examination. A predictable distribution of lesions in dogs with pancreatitis could increase diagnostic accuracy and also further elucidate the pathogenesis of this poorly characterized disease process in the dog.

Materials and Methods

Seventy-three pancreata were collected consecutively from dogs presented for postmortem examination to the Pathology Service at the Animal Medical Center (AMC). All dogs met the study-inclusion criteria of having an antemortem frozen serum sample collected and having the pancreas removed in its entirety within 6 hours of death. Fixation of the pancreas in 10% buffered formalin within the 6-hour period eliminated postmortem degeneration and autolysis of the pancre-
Localization of Pancreatitis

Fig 1. Sequential trimming grid of a formalin-fixed pancreas from a dog. Black lines indicate the sites for sectioning and are separated by 2-cm intervals.

Fig 2. This photomicrograph depicts neutrophilic inflammation (white arrow) and peripancreatic fat necrosis (black arrow) in a dog with suppurative pancreatitis. The lack of fibrosis suggests that this dog most likely had acute pancreatitis. Hematoxylin-eosin stain; 400×.

Acute tissue. The right limb was identified with a suture at the time of removal. All pancreata were weighed and their total length recorded. Additionally, the presence of gross pancreatic lesions was recorded. Pancreata were sectioned every 2 cm, beginning at the tip of the right limb (Fig 1). Each section was processed routinely, stained with hematoxylin and eosin, and evaluated by light microscopy.

A single pathologist (S.J.N.) reviewed all slides from each pancreas for the presence of suppurative inflammation (SI), pancreatic necrosis (PN), LI, and pancreatic fibrosis (F). The percentages of sections with SI, PN, LI, or F were determined. SI was defined as the presence of neutrophils within the pancreatic parenchyma or the surrounding peripancreatic adipose tissue (Fig 2). PN was defined as cellular necrosis...
of pancreatic parenchyma or, more commonly, the surrounding peri-
pancreatic adipose tissue (Fig 2). LI was defined as the presence of a
lymphocytic infiltrate principally within the pancreatic parenchyma or
the periductular interstitial tissues (Fig 3). F was defined as the pres-
ence of increased quantities of fibrous connective tissue within the
pancreatic parenchyma. The presence or absence of F was determined
in the 47 pancreata that had evidence of SI, PN, or LI.

Pancreata were divided into right (60% of total length) and left
limbs (40% of total length; Fig 4) according to previously reported
experiments in Beagle dogs, and the presence of SI, PN, LI, and F
was assessed for each limb. Additionally, pancreata were divided into
5 anatomic regions of equal length, and the presence of SI, PN, and
LI in those 5 regions also was assessed (Fig 5). The tendency for a
preferred location for each type of lesion was evaluated by chi-square
analysis.

**Results**

The mean weight of the 73 pancreata was 41 g (range,
4.2–171.7 g) and the mean length was 25.3 cm (range,
10.4–52.6 cm). Gross lesions suggestive of pancreatitis
were seen in 4 of 73 (5.5%) pancreata. This finding cor-
related with histologic lesions of necrosis and SI in 1 dog;
PN, SI, and F in 2 dogs; and PN, SI, LI, and F in 1 dog.
In contrast, of the 73 pancreata examined, a total of 47
(64.4%) revealed microscopic evidence of PN, SI, or LI.
Twenty-four dogs (51.1%) had SI, 23 dogs (48.9%) had PN,
and 34 dogs (72.3%) had LI. Of the 47 dogs with SI, PN,
or LI, 28 (59.6%) had F. Twenty-three dogs (48.9%) had
SI and PN, 12 of which had F. Eleven dogs (23.4%) had SI
and LI, 6 of which had F. Ten dogs (21.3%) had LI and
PN, 5 of which had F. Finally, 10 dogs (21.3%) had SI, PN,
and LI, 5 of which had F.

In all examined sections of the pancreas, evidence of SI
was seen in only 4 (16.7%) dogs, PN in 1 (4.3%) dog, and
LI in 6 (17.1%) dogs. Involvement of <25% of all sections
was seen in 8 (33.3%), 7 (34.8%), and 24 (66.7%) pancre-
ata, respectively. On average, SI was observed in 45%, PN
in 42.3%, and LI in 30.2% of all sections from dogs with
pancreatitis. Chi-square goodness-of-fit test determined ran-
dom distribution of SI, PN, or LI between the right and the
left limb of the pancreas (P = .43) and among the 5 ana-
tomic regions (P = .45). The number of affected regions
for each of SI, PN, and LI are presented in Table 1.

Only 1 of the 4 dogs with gross lesions of pancreatitis
was suspected of having pancreatitis clinically. Of the 43
dogs with histologic changes of pancreatic inflammation or
necrosis, the primary postmortem examination diagnoses
included the following (in decreasing order of prevalence):
neoplasia (n = 16), neurologic disease (n = 3), hepatic
disease (n = 3), respiratory disease (n = 2), renal disease
(n = 6), heart disease (n = 5), shock or sepsis (n = 1),
gastrointestinal disease (n = 4), thromboembolism (n = 2),
disseminated intravascular coagulation (n = 4), and crypt-
tococcosis (n = 1).

**Discussion**

Pancreatitis is a common disease in both human beings
and dogs. In human beings, it has been estimated that
approximately 90% of all cases of pancreatitis remain un-
diagnosed. Similarly, in dogs, the diagnosis of pancreatitis
is somewhat elusive, especially in mild or subclinical cases.
To better assess the histologic localization of pancreatitis
lesions in dogs, pancreata obtained within 6 hours of death
from dogs submitted to the AMC postmortem-examination
service were examined by light microscopy after routine
processing of multiple sections. Gross lesions were rarely
Localization of Pancreatitis

Fig 4. This diagram depicts a 60:40 length ratio for the right and left pancreatic limbs as previously reported. Modified and reprinted with permission from: Shively MJ. Veterinary Anatomy—Basic, Comparative, and Clinical. College Station, TX: Texas A&M Press; 1984.

recorded (4 of 73, or 5.5%), but when present they correlated with PN and SI in 1 dog; PN, SI, and F in 2 dogs; and PN, SI, LI, and F in 1 dog. This finding strongly suggests that the lack of gross lesions during exploratory laparotomy does not exclude the presence of pancreatitis. Pancreatitis was suspected clinically in only 1 of the 4 dogs with gross lesions of the pancreas. The significance of the gross changes in the remaining dogs is not known, but ex-

Fig 5. This diagram depicts the 5 regions (20% increments) used for lesion localization and statistical analysis. Modified and reprinted with permission from: Shively MJ. Veterinary Anatomy—Basic, Comparative, and Clinical. College Station, TX: Texas A&M Press; 1984.
ploratory laparotomy and surgical biopsy would in all like-
lihood have resulted in an antemortem diagnosis of pan-
creatitis. In contrast, light microscopic lesions of pancreatitis were recorded in an unexpectedly large number of dogs (64%). The inability to detect concurrent gross lesions was thought to be because of the minimal extent of the micro-
scopic changes and the discrete localization of these lesions.

It is surprising that over half of the dogs that were submit-
ted for postmortem examination with a variety of clinical
presentations had some evidence of pancreatic inflamma-
tion or necrosis in at least 1 section of the examined pan-
creas, suggesting that histologic pancreatitis and subclinical
disease may be quite prevalent. This finding also suggests
that examination of multiple sections may be necessary to
document the presence of subtle pancreatic lesions, a prac-
tice not followed in routine diagnostic pathologic because it
is cost prohibitive and, more importantly, may be detri-
mental to the patient. Additionally, this situation presents a
dilemma for confirming subclinical disease based on sur-
gical biopsy samples obtained during a surgical exploration,
because there are few gross indicators to the surgeon to
assist in sample selection. Biopsy of grossly affected tissues
would be expected to correlate with histologic findings con-
sistent with pancreatitis, as was the case in 4 of 4 (100%)
dogs in our study.
LI and F were most commonly detected, followed by SI
and PN. These findings were surprising because LI and F
are more commonly seen with chronic pancreatitis, which
is thought to occur much less frequently in the dog than
does acute pancreatitis.1 It is unknown how many pancre-
atic sections were assessed in the previous study of pan-
creatitis in dogs,1 but it is unlikely that the number of sec-
tions examined was similar to that examined in this study.
Thus, it appears possible that localized areas of LI were
missed in some dogs examined in the previous study, ac-

The inability to detect concurrent gross lesions was thought to be because of the minimal extent of the microscopic changes and the discrete localization of these lesions. It is surprising that over half of the dogs that were submitted for postmortem examination with a variety of clinical presentations had some evidence of pancreatic inflammation or necrosis in at least 1 section of the examined pancreas, suggesting that histologic pancreatitis and subclinical disease may be quite prevalent. This finding also suggests that examination of multiple sections may be necessary to document the presence of subtle pancreatic lesions, a practice not followed in routine diagnostic pathology because it is cost prohibitive and, more importantly, may be detrimental to the patient. Additionally, this situation presents a dilemma for confirming subclinical disease based on surgical biopsy samples obtained during a surgical exploration, because there are few gross indicators to the surgeon to assist in sample selection. Biopsy of grossly affected tissues would be expected to correlate with histologic findings consistent with pancreatitis, as was the case in 4 of 4 (100%) dogs in our study.

LI and F were most commonly detected, followed by SI and PN. These findings were surprising because LI and F are more commonly seen with chronic pancreatitis, which is thought to occur much less frequently in the dog than does acute pancreatitis. It is unknown how many pancreatic sections were assessed in the previous study of pancreatitis in dogs, but it is unlikely that the number of sections examined was similar to that examined in this study. Thus, it appears possible that localized areas of LI were missed in some dogs examined in the previous study, accounting for the lower prevalence of LI reported. These potentially contradictory findings between studies may be explained by the more localized distribution and the more subtle nature of the LI observed here. LI alone may not constitute pancreatitis or clinically relevant inflammation but rather could represent an age-related accumulation of lymphocytes that provide antigen surveillance for epithelial tissues. LI was not consistent in all dogs, and, more importantly, the accumulation of lymphocytes was localized rather than diffuse. Consequently, we believe its presence is noteworthy. For the purpose of this study, increased numbers of lymphocytes in the pancreatic parenchyma were considered indicative of LI. The potential reasons for increased lymphocyte numbers include antigen surveillance by lymphocytes, a form of early chronic pancreatitis (especially in those sections with accompanying F), or a precursor lesion of pancreatic acinar atrophy (PAA). In predisposed breeds (German Shepherd Dogs and Rough-Coat-
ed Collies), marked LI at the border of affected and unaf-
fected tissue is characteristic of subclinical exocrine pancreatic insufficiency and can progress to marked paren-
chymal atrophy with a less-marked lymphocytic response. However, these predisposed breeds were not represented in our study population, and thus it appears unlikely that the LI in these dogs was a precursor lesion to PAA.

Thirty-four dogs had LI and 22 (64.7%) of these dogs had accompanying F; a combination of histopathologic find-
ings traditionally classified as chronic pancreatitis. However, 12 dogs (35.3%) had LI without any evidence of F In contrast to previous perceptions, this finding suggests either that acute pancreatitis can be lymphocytic or that the biopsy samples were collected early in the development of chronic pancreatitis before F had developed. Additional studies are required to answer this question conclusively.

SI and PN were the most common lesions noted and were considered to represent the classic pattern of changes associated with ANP. However, several of the affected dogs (12) also had F leading to a diagnosis of chronic pancreatitis in these instances. This finding suggests that chronic pancreatitis is not exclusively associated with LI and that both acute and chronic pancreatitis can be severe as indicated by the presence of PN.

Surprisingly, the second most common combination was that of SI and LI. As the inflammatory response matures, this mixture of cellular infiltrates would be expected and may represent a continuum. This finding was followed equally by both LI and PN and the combination of all 3 types of lesions. This observation suggests that it is rare to identify the full spectrum of acute and chronic lesions within the same pancreatic specimen. It also suggests that although some lymphocytic aggregation within the pancreas may occur with age, LI occurs as an integral part of many other pancreatic processes and therefore is a relatively common tissue response to various insults.

The 3 changes, (SI, PN, and LI), did not occur in any preferred limb or anatomic region of the pancreas, and the lesions were most consistently seen in discrete areas rather than diffusely throughout the organ. LI was more localized than either SI or PN, and 55.9% of pancreata with LI lesions had those lesions in only 1 of 5 anatomic regions, whereas only 16.7% of pancreata revealed SI lesions and 17.4% of pancreata revealed PN lesions in 1 of 5 anatomic regions.

Earlier reports noted a propensity for pancreatitis lesions to be localized around the main pancreatic duct and its orifice into the duodenum, but this observation was not confirmed in the current study. Retrograde passage of pancreatic secretions into the parenchyma may be one mechanism by which periductular tissue injury is produced in pancreatic ductular obstructive disease in dogs. Experimental retrog-

<table>
<thead>
<tr>
<th>No. of Affected Regions</th>
<th>SI</th>
<th>PN</th>
<th>LI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

SI, suppurative inflammation; PN, pancreatic necrosis; LI, lympho-
cytic inflammation.
Localization of Pancreatitis

left-lobe disease with only a moderate effect on the right pancreatic lobe. This may be related to ductal anastomoses between the right and the left lobes. The lesion distribution in our study was such that very few animals had diffuse changes. Rather, only a small number of animals had involvement of all sections. In many more dogs, <25% of the total number of sections was affected. The distribution of the lesions observed here differs from that described for the obstructive model of pancreatitis. Consequently, we speculate that obstructive disease is not a major cause of spontaneous pancreatitis in the dog.

Our findings suggest that SI, PN, or LI is common in the dog. Macroscopic findings of pancreatitis are extremely uncommon, and lack of such findings during exploratory laparotomy, for example, does not exclude histologic pancreatitis. Furthermore, pancreatitis lesions, especially LI, often are localized, and a single biopsy sample is insufficient to exclude histologic pancreatitis. No preferred site for biopsy collection could be identified. Multiple sections of pancreas should be examined at postmortem examination to comprehensively assess the exocrine pancreas for necrosis or inflammatory changes. Randomly distributed lesions and subclinical disease are prevalent in dogs presented for postmortem examination for a variety of other neoplastic, degenerative, or inflammatory processes.

Acknowledgments

We wish to acknowledge the Morris Animal Foundation for financial support of this project. Special thanks to Richard Luong for technical assistance with photography. This project was presented in part at the American College of Veterinary Internal Medicine Forum, Raleigh, NC, June 2003.

References