Pancreatitis: A Forensic Perspective

James R. Gill

ABSTRACT

Among the numerous etiologies of acute and chronic pancreatitis, several underlying causes (e.g., chronic alcohol abuse, trauma, medical therapy) may result in a death that is reportable to the medical examiner/coroner. As such, forensic pathologists are likely to encounter pancreatitis at autopsy and therefore must be familiar with its etiologies, mechanisms of death, autopsy findings, and medicolegal investigation. This review will focus on the aspects of pancreatitis that may be useful to forensic pathologists in their daily practice. This includes determining if acute or chronic pancreatitis caused or contributed to death as well as determining the etiologically specific proximate cause of death. Current theories of how these various processes result in inflammation of the pancreas are reviewed. *Acad Forensic Pathol.* 2016 6(2): 237-248

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INTRODUCTION

Acute pancreatitis is a reversible inflammatory lesion due to a variety of causes (1-15). The investigative goal for the forensic pathologist is to determine the etiology of the pancreatitis and if it contributed to or caused death. The clinical history and gross and microscopic findings are keys to the diagnosis. The incidence and causes of pancreatitis shows great variation from country to country. In Western countries, the incidence of pancreatitis is approximately 10 to 20 instances per 100 000 population and the most common causes are biliary disease (gallstones) and chronic alcoholism (16). Certain medications and trauma also may cause it. Recurrent episodes of acute inflammation may scar and damage the pancreas, resulting in chronic pancreatitis (17-19). This chronic damage may impair the endocrine and exocrine abilities of the pancreas (20-23). Injury of the exocrine pancreas may result in malabsorption due to insufficiency of secretion of digestive enzymes (e.g., trypsin, lipase, amylase, elastase). Damage to the endocrine pancreas may result in insulin insufficiency with hyperglycemia and the need for insulin therapy.

This review will focus on the aspects of pancreatitis that may be encountered by forensic pathologists in their daily practice: the autopsy pathology of pancreatitis, etiologies including the role of ethanol, complications and mechanisms of death, and death certification. Current theories of how various processes may cause pancreatitis are discussed.

DISCUSSION

Acute Pancreatitis

Pathophysiology

There are numerous causes of acute pancreatitis (22-44) (**Table 1**) including alcohol ingestion, biliary tract disease (gallstones/malignancy), surgery/postoperative states (45), trauma (36), metabolic disorders (hypertriglyceridemia, hypercalcemia)(46-49), infections (adenovirus, mumps, ascariasis, mycoplasma) (44, 50), and drugs (the most common include thiazides, sulfa, methyldopa, and procainamide) (51, 52). Malignancies of the pancreas and bile ducts may result in pancreatitis due to obstruction/stenosis of the exo-

Table 1: Causes of Pancreatitis

Common Causes
Chronic alcoholism
Cholelithiasis
Post endoscopic retrograde cholangiopancreatography (ERCP)
Trauma
Drugs (azathioprine, sulfonamides, gliptins, sulindac, tetracycline, valproic acid, didanosine, methyldopa, estrogens, furosemide, 6-mercaptopurine, pentamidine, 5-aminosalicylic acid compounds, corticosteroids, octreotide, procainamide, thiazides)
Idiopathic
Less Common Causes
Obesity
Infection (mumps, coxsackie B viruses)
Hyperlipidemia
Hypercalcemia (hyperparathyroidism)
Hyperthyroidism
Malignancy
Surgery

crine pancreatic ducts (53-57). Autodigestion caused by inappropriate intrapancreatic (instead of intestinal) activation of endogenous proteolytic enzymes has been proposed. Support for intracellular zymogen activation comes from basic research on genetically engineered mice and the clinical use of protease inhibitors to prevent pancreatitis. Since proteases are involved in activation of pancreatic enzymes, protease inhibitors, which block proteolytic cleavage of protein precursors, were theorized to prevent pancreatitis. Studies have demonstrated that patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) who were pretreated with a protease inhibitor had a reduced incidence of ERCP-related pancreatitis (58). Obstruction/hypersecretion and the “common channel” hypothesis in which reflux of bile into the pancreatic duct causes activation of the enzymes also has been studied (59).

Premature activation of digestive enzymes in the acinar cells has been demonstrated in experimental models (using mice that lack trypsinogen 7) to result in approximately 50% of acinar cell death (60). Thus, approximately half of the acinar damage during pancreatitis appears to occur independently of pathologic trypsinogen activation and is believed to result from a second mechanism that drives local and systemic inflammation. This second mechanism may involve NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), which is a protein complex that controls transcription of DNA, cytokine production, and cell survival. NF- κ B activation is believed to lead to the production of inflammatory mediators that elicit local inflammation (thereby causing further pancreatic damage) and then lead to widespread systemic inflammation (60). Trypsin also activates prekallikrein (and the kinin system thus affecting the inflammatory system) and Hageman factor (factor XII), thus affecting the clotting and complement systems.

The initiating event on the acinar cell is some form of pathologic injury that may vary depending upon the specific insult. The mechanisms as to how the pathologic injury results in activation of pancreatic enzymes may occur by three different injury pathways. The first pathway is direct acinar injury due

to physical trauma (e.g., blunt impact), infection by viruses (e.g., mumps), drugs, or other processes that result in pancreatic ischemia (e.g., shock). The second pathway involves pancreatic duct obstruction (e.g., cholelithiasis, tumor, contraction of the sphincter of Oddi (at the ampulla of Vater) by the effects of ethanol). Blockage results in the accumulation of the enzyme rich pancreatic fluid, which contains lipase (which is secreted in active form) that results in local fat necrosis with subsequent inflammation. The inflammatory process results in edema, compromise of blood flow, and ischemic injury to the acinar cells. The third pathway involves problems with intracellular transport of the inactive zymogens within acinar cells. Defective packaging and release of enzymes has been demonstrated with pancreatic duct obstruction and alcohol intoxication. Due to chaotic cellular membrane trafficking, the proenzymes come in contact with lysosomal hydrolases, which results in activation of digestive enzymes in the cell and/or release of secretory vesicles into the interstitium instead of the duct. This pathway also may explain metabolic (e.g., hypercalcemia) pancreatic injury (60-62).

Complications and Mechanisms of Death

Pancreatitis may cause local and systemic complications (22, 63-68). Locally, injury of the pancreas may cause thrombosis, hemorrhage, abscess, or pseudocysts. Systemically, the lungs, cardiovascular system, kidneys, stomach, and coagulation system may be affected (systemic inflammatory response) resulting in adult respiratory distress syndrome (ARDS), shock, pericardial effusion, acute renal tubular necrosis, gastritis, and disseminated intravascular coagulation (DIC). In order to determine if pancreatitis caused or contributed to death, one may consider the above mechanisms of death. When there are competing proximate causes, the mechanism of death may help determine the correct cause.

The systemic inflammatory response syndrome (SIRS) is a nonspecific response to a variety of insults and can be caused by ischemia, inflammation, trauma, and/or infection. It is defined as two or more of the following: fever of more than 38°C (100.4°F) or less

than 36°C (96.8°F), heart rate greater than 90 beats per minute, respiratory rate of greater than 20 breaths per minute or low arterial carbon dioxide tension, and an abnormal white blood cell count. Pancreatitis may cause SIRS leading to shock, DIC, and adult respiratory distress syndrome. Other mechanisms/immediate causes of death due to pancreatitis include pulmonary emboli, electrolyte abnormalities, and secondary bacterial infections (e.g., bronchopneumonia, cholangitis, peritonitis, sepsis).

Clinical and Autopsy Findings

Acute abdominal pain, fever, and an elevated white blood count are common presenting signs and symptoms (69). If a patient with abdominal pain dies before medical evaluation, the differential diagnosis includes acute appendicitis, peptic ulcer disease, acute cholecystitis, bowel ischemia, acute hepatitis, gynecologic causes (ectopic pregnancy, ovarian torsion, pelvic inflammatory disease), diverticulitis, trauma, aortic aneurysm, and bowel obstruction. Blue-gray skin discoloration of the flanks (Grey-Turner sign) and periumbilical area (Cullen sign) are signs of pancreatitis that should not be confused with blunt impact. In fact, pancreatitis due to blunt trauma may have little if any external evidence of injury. Features that may help support the diagnosis of pancreatitis due to trauma include lacerations of the pancreas or adjacent viscera, the circumstances, and/or the presence of other injuries.

Pancreatitis may progress to shock, DIC, and adult respiratory distress syndrome. Hyperglycemia and hypocalcemia are part of the Ranson criteria (**Table 2**), which are clinical parameters used to predict prognosis (70). Imaging and laboratory studies are useful in the clinical diagnosis (71-75). Elevated serum lipase and amylase concentrations are highly sensitive and specific diagnostic markers for acute pancreatitis in the living (75). There is little forensic literature on postmortem analysis of lipase. In general, postmortem enzyme analysis is difficult to perform and interpret due to concentration fluctuations and postmortem changes. Studies in dogs found that postmortem amylase and lipase concentrations remained stable (48-hour interval) and may be beneficial for diagnosing pancreatitis (76). Postmortem amylase and lipase testing usually is not needed, as the autopsy will provide the definitive diagnosis of acute pancreatitis.

At autopsy, the pancreas is swollen, with necrosis and/or hemorrhage (77). Fat necrosis may involve the surrounding pancreatic tissues and the omentum. The pancreas, due to its storage of digestive enzymes, undergoes rapid autolysis after death. The autolyzed pancreas is soft with loss of lobular architecture that may be mistaken for acute pancreatitis. The clinical history usually can distinguish acute pancreatitis from autolysis but histologic examination is useful in questionable instances. Acute inflammation and fat necrosis are diagnostic features of acute pancreatitis (**Imag-**

Table 2: Ranson Criteria for Clinical Diagnosis and Mortality in Nongallstone Pancreatitis (70)

At Admission	Within 48 Hours
1. Age >55 years	1. Serum calcium <2.0 mmol/L (<8.0 mg/dL)
2. White Blood Count >16 000 cells/mm ³	2. Hematocrit decrease >10%
3. Blood glucose >11 mmol/L (>200 mg/dL)	3. Hypoxemia (PaO ₂ <60 mmHg)
4. Serum AST >250 IU/L	4. BUN increased by 1.8 or more mmol/L (5 or more mg/dL) after intravenous fluid hydration
5. Serum LDH >350 IU/L	5. Base deficit >4 mEq/L
	6. Fluid sequestration >6

AST: Aspartate aminotransferase; **LDH:** Lactate dehydrogenase; **BUN:** Blood urea nitrogen

Score ≥3 severe pancreatitis likely

Score (% mortality): 0-2 (2%), 3-4 (15%), 5-6 (40%), 7-8 (100%)

es 1-3). It may be difficult grossly and microscopically to distinguish fat necrosis from fat autolysis (78, 79). The detection of inflammatory cells within the fat or surrounding a degenerating fat nodule would support a diagnosis of fat necrosis as opposed to autolysis. In addition, livor mortis (typically intravascular congestion) involving the pancreas (**Image 4**) should not be mistaken for hemorrhagic pancreatitis (extensive extravasation). Acute inflammation is diagnostic of an antemortem process as there cannot be pronounced inflammation without circulation. As the inflammation progresses, neutrophils will be replaced by lymphocytes and macrophages. Acute pancreatitis may resolve, recur, or progress to chronic pancreatitis.

The key distinction for chronic pancreatitis from acute is irreversible impairment of pancreatic function (see below). The exocrine and/or endocrine components are damaged by the inflammation to an extent that malabsorption/steatorrhea or secondary diabetes mellitus occurs. Instances of acute pancreatitis usually are self-limited and respond with supportive therapy. If the pancreatitis is due to a biliary obstruction, the blockage must be addressed (e.g., surgery, ERCP).

Biliary stones may result in cholangitis as well as pancreatitis. Culture of the bile duct and blood may help diagnose the immediate cause of death if bacterial cholangitis resulted in sepsis. Histological exam, thin gross

Image 1: Acute pancreatitis with neutrophilic infiltrates and acinar necrosis (H&E, x200), higher magnification inset of acute inflammation (H&E, x400).

serial sections of the pancreas, and opening of the biliary tree may reveal an impacted stone or occult malignancy (e.g., pancreatic, cholangiocarcinoma) that is responsible for the pancreatitis. Pancreatitis due to a viral infection (e.g., mumps) is usually diagnosed through clinical history. The mumps virus can be isolated from throat swabs, urine and cerebrospinal fluid. The microorganism has a direct toxic effect on the acinar cell that results in necrosis with inflammation but no fat necrosis. The diagnosis of medication-induced pancreatitis is based on the clinical circumstances and the exclusion of other causes. Certain medications (**Table 1**) have been implicated to cause pancreatitis including several that have resulted in recurrent pancreatitis following a rechallenge with the medication (10).

Ethanol and the Pancreas

How chronic ethanol abuse results in pancreatitis is not entirely known (80-87). Ethanol may cause pancreatitis in a number of ways. Alcohol has an effect on intrapancreatic digestive enzyme activation, by either sensitizing acinar cells to pathologic stimuli or stimulating the release of a secretagogue (cholecystikinin, [CCK]) from duodenal cells (80). Animal models have demonstrated that acinar cells are the initial site of morphologic (necrosis) damage. Interestingly, rats continuously given ethanol do not develop pancreatitis unless there is an additional trigger (e.g., CCK) (88). One theory is that ethanol sensitizes the pancreas to pancreatitis but other factors trigger the process

Image 2: Peripancreatic tissue with fat, fat necrosis, and acute inflammation percolating through adipocytes (H&E, x100).

(e.g., high fat diet, excess cholecystokinin) (88). The properties of acinar cells affected by ethanol include calcium signaling, secretion of zymogens, cellular regeneration, and mitochondrial membrane integrity. Ethanol may result in pancreatic duct contraction (sphincter of Oddi), leading to a similar mechanism seen with duct obstruction due to gallstones. As not everyone who abuses ethanol develops pancreatitis, some have proposed molecular abnormalities that may predispose to pancreatitis (82). Genetic studies have linked a hereditary form of pancreatitis to trypsinogen mutations (89).

Chronic Pancreatitis

Acute pancreatitis from a variety of causes may lead to chronic pancreatitis (1, 18, 21-23, 25). Chronic alcoholism is the most common cause (29, 41). Other etiologies include chronic pancreatic duct obstruction/stenosis (e.g., neoplasms, calculi, trauma, pseudocysts), cystic fibrosis, and other rare infectious and congenital (e.g., pancreas divisum) causes (30). With repeated bouts of inflammation, the pancreas may be irreversibly damaged which impairs the exocrine and, usually later in the course, endocrine functions.

Image 3: Autolyzed pancreas with diffuse “coagulopathic” change without inflammation (H&E, x100).

Pseudocysts (localized fluid collections) are a complication of pancreatitis (66, 90, 91) that may appear several weeks after the onset of pancreatitis. Pancreatic duct and/or pseudocyst drainage and Whipple resections may relieve the pain associated with chronic pancreatitis. Diabetes mellitus and malabsorption are potential long-term complications (63, 64) and chronic pancreatitis has been associated with an increased risk of pancreatic cancer (92).

Clinical and Autopsy Findings

Weight loss, abdominal pain, low serum protein, and edema are common presenting signs and symptoms. Hyperglycemia (impaired glucose tolerance) and signs of malabsorption (steatorrhea) are common (20).

The classic triad for chronic pancreatitis is pancreatic calcification, steatorrhea, and diabetes mellitus. Radiological studies of the pancreas may demonstrate fibrosis, calcifications, and pseudocysts (71).

At autopsy, the pancreas is firm (increased fibrosis) with visible calcification (90, 91, 93). The ducts may be dilated and contain concretions. Pseudocysts containing pancreatic secretions such as amylase, have a non-epithelialized wall of fibrous and granulation tissues (63, 91, 93). Microscopically, the pancreas has a loss of acini with relative sparing of islets, parenchymal fibrosis, and variable duct dilation (**Image 5**) (78, 79). There is a chronic inflammatory infiltrate and the dilated ducts may contain inspissated eosinophilic concretions.

Image 4: Pancreas with congested vessels that may grossly mimic hemorrhagic pancreatitis (H&E, x100).

Death Certification

When acute and/or chronic pancreatitis is the immediate cause of death, it usually has an etiologically specific underlying cause. In approximately 10-25% of instances, no cause is diagnosed (idiopathic) (16). Biliary sludge, passed gallstones, and genetic causes due to inherited alterations in genes encoding pancreatic enzymes (e.g., cationic trypsinogen [PRSS1]) may explain some of these instances (89).

The vast majority of pancreatitis deaths are certified with a natural manner and may not even be reported to or accepted by the medical examiner/coroner for in-

vestigation. If the acute pancreatitis, however, is due to a medication or if death occurred due to a predictable complication of an appropriate procedure (e.g., pancreatitis caused by an elective endoscopic procedure), the death may be reportable and the manner may be classified as therapeutic complication (where available), natural, or accident depending upon the local practice (94). Pancreatitis due to known or suspected blunt force trauma to the abdomen, especially in instances of acute pancreatitis in children, needs further investigation. If the pancreatitis is due to trauma, the manner of death will be dictated by the circumstances of the injury and may include homicide.

Image 5: Chronic pancreatitis with fibrosis, lymphocytic infiltrates, and isolated glands/ducts (H&E, x40).

SUMMARY

The following are autopsy, investigative, and certification tips and pitfalls:

1. Posterior lividity of the pancreas may mimic hemorrhagic pancreatitis.
2. A careful dissection of the biliary tree may reveal a stone or malignancy.
3. Microbiological culture of purulent material in the biliary tree may be useful.
4. An occult malignancy may be missed in an apparent chronic pancreatitis.
5. Consider traumatic causes and assess for associated bowel and mesenteric injury.
6. Determine the etiology (underlying cause) of the pancreatitis.
7. Test the vitreous for glucose, as hyperglycemia may be the immediate cause of death.

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