MEDICAL RADIOLOGY

Diagnostic Imaging

A. L. Baert
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Imaging of the Pancreas

Acute and Chronic Pancreatitis

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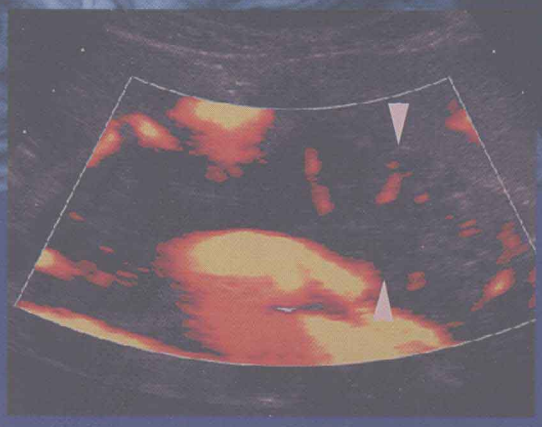
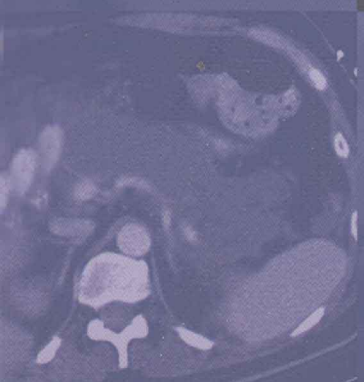
Editors





Springer

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E. J. Balthazar · A. J. Megibow · R. Pozzi Mucelli (Eds.)

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With 335 Figures in 873 Separate Illustrations, 69 in Color and 47 Tables

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MEDICAL RADIOLOGY

Diagnostic Imaging

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Dedication for

Professor Carlo Procacci
(1950–2004)

Scholar, leader, friend.

Foreword

This second volume on modern multimodality pancreatic imaging deals with acute and chronic pancreatitis and pancreatic trauma. It comprehensively covers the diagnostic and interventional radiological techniques employed today in the management of patients with lesions related to one of these conditions.

As with the first volume, which deals with cystic and rare tumors of the pancreas, the various chapters are written by authors from both sides of the Atlantic, all internationally recognized experts in their particular field of interest. Their contributions, illustrated by high-quality images and figures, represent the state-of-the-art methods in pancreatic radiology.

I am particularly indebted to the editors, E. J. Balthazar, A. J. Megibow and R. Pozzi-Mucelli, for their great efforts in preparing this superb volume, which should be considered as the standard reference handbook on imaging of acute and chronic pancreatitis and pancreatic trauma for general and abdominal radiologists, gastroenterologists and abdominal surgeons. It will undoubtedly be of great help to guide them in the correct diagnostic and therapeutic decisions for their patients.

I am particularly grateful to R. Pozzi-Mucelli, who kindly accepted to take over the editor's task from our sadly deceased C. Procacci.

I am convinced that this outstanding work will meet with the same success as the first volume on cystic and rare tumors of the pancreas previously published in this series.

Leuven

Albert L. Baert

Preface

Pancreatitis is a ubiquitous disease. Although it is more prevalent in developed countries, accounting for approximately 210,000 yearly hospital admissions in the US, the wide variety of causes accounts for it being seen in every country. Even though it is an old affliction, its clinical and pathologic manifestations were not recognized until late in the 19th and early 20th century. Seminal articles by CHIARI (1896), FITZ (1889) on acute pancreatitis and COMFORT 1946 on chronic pancreatitis defined the distinctive features of these related but separate clinical entities.

The radiologic evaluation of patients with these disorders paralleled the increasing clinical sophistication and, important to our current volume, the rapid technological advances as related to imaging. The modern era of pancreatic imaging began with the introduction of gray-scale ultrasound in the early 1970s and computed tomography (CT) in the mid 1970s. Pancreatic imaging progressed rapidly in the last two decades of the 20th century, specifically related to the appreciation of information provided by the proper use of iodinated intravenous contrast materials for both CT and magnetic resonance imaging (MRI). The development of multidetector-row CT (MDCT), advances in MRI beyond spin-echo techniques and of endoscopic ultrasound further improved and accelerated this trend. In addition to improving imaging diagnosis of pancreatitis and its complications, imaging techniques serve as a platform for increasingly innovative minimally invasive interventional therapies.

The present volume describes and illustrates the contributions, strengths and limitations of state-of-the-art imaging modalities used to diagnose and evaluate patients with pancreatitis and its abdominal complications. Additionally, we attempt to frame the imaging contributions in the context of what information is needed to make clinical decisions. The reader will notice several unavoidable overlapping opinions reflecting different points of view, distinct idiosyncratic experiences and various conflicting bibliographic references. This serves our purpose in providing a compendium of a variety of approaches to these complex patients. We are indebted to our eclectic experts, all recognized and experienced pancreatologists from Europe and the US, who contributed to this monograph.

This project has taken a significantly longer time to bring to publication than originally intended. While the editors bear the ultimate responsibility for timeliness of final publication, the effect of the untimely death of Professor Carlo Procacci of Verona cannot be minimized. The cruel irony that Professor Procacci was taken from us by pancreatic cancer is not lost. Professor Procacci conceived this project in 2000; he succumbed to his disease on January 1, 2004 at far too young an age. The appointment of Professor Roberto Pozzi-Mucelli at the Policlinico G. Rossi is guaranteed to sustain the contributions of this center to the world's knowledge of pancreatic disease.

A special note of thanks goes to our publisher, Springer-Verlag, to our editor, Ursula Davis, whose patience is truly remarkable, to the copy editors who worked hard to prepare the manuscripts and assure the illustrations are of the highest quality, and finally to Professor Albert Baert, who along with Professor Klaus Sartor are the "Diagnostic Imaging" series editors. Professor Baert's gentle and kindly encouragements along the way never failed to remind us of his belief in the potential value of this particular work.

New York — Emil J. Balthazar
New York — Alec J. Megibow
Verona — Roberto Pozzi Mucelli

Chiari H (1896) Ueber Selbstverdauung des menschlichen Pankreas. Zeitschrift fuer Heilkunde 17:69–96

Comfort MW, Gambill EE. Baggentoss AH (1945) Chronic relapsing pancreatitis: a study of twenty-nine cases without associated disease of the biliary or gastro-intestinal tract. Gastroenterology 4:239-85, 376–408

Fitz RH (1889) Acute pancreatitis: a consideration of pancreatic hemorrhage, hemorrhagic, suppurative, and gangrenous pancreatitis, and of disseminated fat necrosis. Boston Med Surg J 120:181–187

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Acute Pancreatitis

Pathophysiology of Acute Pancreatitis

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1.1 Introduction

Acute pancreatitis is a common clinical entity that follows a variable course ranging from mild abdominal pain to multisystem organ failure and death. There are numerous known causes of acute pancreatitis, all of which are thought to precipitate the disease by causing acinar cell injury. Although acinar injury may be a common trigger for pancreatitis, the mechanisms linking causal entities to induction of cellular injury remain unclear. Similar to the variability of clinical presentation, the pattern of pancreatic pathology following injury can manifest in many ways including: simple edema, necrosis, pseudocysts, and abscesses.

1.2 Etiology

Acute pancreatitis can be triggered by a mechanical, metabolic, vascular, or infectious event (Table 1.1). Although the molecular mechanisms responsible for the induction of pancreatitis for each of these causes remain elusive, leading theories have been gaining evidence and will be discussed subsequently. Gallstone disease and chronic ethanol abuse account for greater than 80% of cases of acute pancreatitis; however, the incidence of pancreatitis in patients with these conditions is low (5%–10%) suggesting that additional co-factors are necessary to precipitate pancreatitis. Idiopathic causes are common and apply to patients with confirmed pancreatitis in which a causative agent cannot be identified. Regardless of the etiology, the clinical manifestations of acute pancreatitis are remarkably similar, suggesting that the pathogenesis involves a common pathway.

Table 1.1. Etiologies of clinical acute pancreatitis. [Modified from Cappell (2008); Greenberger and Toskes (2008)]

Common etiologies
• Biliary calculi and sludge (Sect. 1.2.1.1)
• Alcoholism (Sect. 1.2.2.1)
• Hypertriglyceridemia (Sect. 1.2.2.2)
• Endoscopic retrograde cholangiopancreatography
• Traumatic Pancreatitis
Drug-induced (Sect. 1.2.3)
• Azathioprine
• 6-MP
• Sulfonamides
• Estrogens
• Tetracycline
• Anti-epileptic
• Anti Retroviral
• Furosemide
Hypercalcemia with or without hyperparathyroidism (Sect. 1.2.2.3)
Posterior penetrating duodenal ulcer
Scorpion venom
Uncommon etiologies
• Ischemia/vasculitis (hypoperfusion)
• Pancreatic cancer (histologic evidence is present in many cases)
• Pancreas divisum
Genetic/hereditary (Sect. 1.2.3)
Cystic fibrosis
Infections (Sect. 1.2.3)
• Ascariasis
• Mumps
• Coxsackievirus
• Herpetic/CMV (HIV patients)

1.2.1 Mechanical Etiology

The common inciting event in pancreatitis with a mechanical etiology is pancreatic duct obstruction. Gallstones, tumors, pancreas divisum, ascariasis, and trauma can all result in obstructive pancreatitis. Pancreatic ductal epithelial cells function to convey digestive enzymes in an inactive zymogen state from acinar cells to the duodenum where the enzymes are cleaved to an active form by enterokinase. Cells that line the pancreatic ducts secrete water, bicarbonate, and mucus to minimize activation of the transported enzymes. Fat and protein in the duodenum induce cholecystokinin (CCK) secretion from small intestine mucosal endocrine cells, which in turn leads to the release of inactive digestive enzymes from the acinar cells. When the pancreatic duct is obstructed, acinar cells continue secreting digestive enzymes against a closed system. It is thought that ultimately, intrinsic protective mechanisms to prevent zymogen activation are overwhelmed, resulting in the premature activation of the digestive enzymes, which in turn leads to acinar cell injury and pancreatitis. (Grady et al. 1992; Sakorafas and Tsiotou 2000; Lightner and Kirkwood 2001).

1.2.1.1 Biliary Calculi

It is generally accepted that gallstone-induced pancreatitis results from a gallstone migrating through the ampulla of Vater. Several mechanisms have been proposed to explain how the migrating stone can cause inflammation of the pancreas. The most likely explanation for the pathogenesis of gallstone pancreatitis is that as stone passes through the ampulla it either directly occludes the pancreatic duct by impaction or indirectly leads to pancreatic duct hypertension by creating inflammation and edema of the ampulla as the stone passes (Moody et al. 1990). Other theories that have been put forth suggest that bile reflux into the pancreatic duct activates pancreatic enzymes and leads to pancreatic inflammation. The once popular common channel hypothesis suggested that a stone impacts in the ampulla causing bile to reflux through the common channel that exists between the distal ends of the pancreatic and common bile ducts (CBD) has been called into question because normally there is higher resting pressure in the pancreatic duct compared to the CBD. Additionally, pancreatic zymogens are activated by bile only after at least 8–12 h of incubation time. There are also reports that 20% of the general population has separate common bile duct and pancreatic duct openings (Arendt et al. 1999).

A study examining potential unidentified causes of idiopathic acute pancreatitis found that 73% of these patients had biliary sludge or microlithiasis. The authors hypothesized that over 75% of idiopathic attacks of acute pancreatitis are, in fact, caused by microscopic gallstones that were not detected using standard radiological techniques (Ros et al. 1991). Treating these patients with cholecystectomy has proven to decrease the rate of recurrence of acute pancreatitis, suggesting that the rates of gallstone pancreatitis may be globally underestimated.

1.2.1.2 Pancreatic Obstruction from Neoplasm and Ascariasis

Pancreatic neoplasms cause approximately 3% of acute pancreatitis cases with a wide range of severity. The etiology of neoplasm-associated pancreatitis

is thought to result from an obstructed or stenotic pancreatic duct that leads to an increase in pressure distal to the obstruction. Evidence suggests that any pancreatic lesions, benign, malignant, solid or cystic can be a potential cause of pancreatitis. Thus, neoplastic lesions of the pancreas must be considered in all idiopathic cases, it is important to note the potential requirement for repeat imaging after the acute inflammation has resolved as surrounding inflammation makes CT diagnosis of a carcinoma more difficult (Grendell 1990).

It should be stressed that any insult which causes obstruction of the pancreatic duct can induce acute pancreatitis. For example, ascariasis, the most common helminth worldwide, is the second most common cause of acute pancreatitis in India. The worms move into the ampulla and block drainage from both the pancreatic and CBD. It is rare to find pancreatic duct invasion by ascariasis, due to the narrow duct lumen. Presence of ascariasis can be diagnosed by ultrasound demonstrating tubular structures in the ducts and ERCP can aid in the diagnosis and extraction of invading worms (Khuroo et al. 1992).

1.2.1.3 Congenital Anomalies – Pancreas Divisum

ERCP and autopsy studies demonstrate pancreas divisum in up to 10% of the population. Pancreas divisum occurs when non-fusion of the dorsal and ventral ducts results in a dominant dorsal duct that collects the majority of pancreatic secretions and drains through a patent minor papilla. The smaller ventral duct collects secretions from the inferior portion of the head of the pancreas and the uncinate process and drains via the ampulla of Vater. Several clinical studies support the conclusion that pancreas divisum predisposes some patients to acute pancreatitis, but the majority of patients with pancreas divisum have no symptoms throughout their lifetime, in fact it is estimated that only 5% of patients with pancreas divisum develop acute pancreatitis. One hypothesis about the etiology of pancreatitis resulting from pancreas divisum is that in the setting of a stenotic lesser papilla successful pancreatic drainage does not occur, resulting in a relative pancreatic duct obstruction. Some reports suggest that stenting the duct of Santorini can decrease the frequency of attacks of pancreatitis in these individuals (Sakorafas and Tsiotou 2000). In the absence of severe pancreatitis no therapeutic maneuvers are indicated for pancreatic divisum. If the pancreatitis is severe or there are multiple attacks, then the minor papilla may need to be stented, surgical drainage may be required, or sphincterotomy may be indicated (Grendell 1990).

1.2.1.4 Trauma

Trauma to the pancreas results from iatrogenic and external traumatic causes. Post-procedural pancreatitis can be caused by direct manipulation of the pancreas or the pancreatic duct. ERCP has a 3%–4% pancreatitis rate. If the patient has a minor papilla and an accessory pancreatic duct, these rates decrease. Of the complications that occur after ERCP 59% are mild complications, 32% are moderate, 7% are severe, and 2% are fatal. Post-ERCP pancreatitis is thought to occur when more contrast is injected than the duct can hold. Furthermore, there is animal evidence that the iodinated contrast materials, as used in imaging studies, can contribute to the severity of acute pancreatitis (Trap et al. 1999; Pezzilli et al. 2002). Factors that increase the risk of post-ERCP pancreatitis are: prior history of pancreatitis, operator inexperience, elevated injection pressures, multiple injections into the pancreatic duct, and depth of cannulation into the pancreatic duct. External pancreatic trauma, often undetected at the time of injury, can result in ductal strictures that manifest years later with chronic obstructive pancreatitis.

1.2.2 Metabolic Etiology

The common metabolic etiologies that can cause pancreatitis include excess ethanol use, hyperlipidemia, hypercalcemia, and medications.

1.2.2.1 Alcohol

There is no universally accepted hypothesis explaining the etiology of alcoholic pancreatitis. Symptoms usually develop between 2 and 10 years after initiation of heavy drinking, but acute pancreatitis can develop in some patients following brief exposure. Patients that develop alcohol-induced acute pancreatitis average a daily consumption of 100–150 g of alcohol. It has been established that the type of alcoholic beverage does not affect the risk of developing pancreatitis or the presentation of the disease

(Wilson et al. 1985). Despite the clear connection between alcohol consumption and pancreatitis, only 10%–15% of heavy alcohol users develop the disease, suggesting additional co-factors are required to trigger an attack of pancreatitis. One theory of the etiology of alcohol-induced pancreatitis is that oxidative metabolism of ethanol by alcohol dehydrogenase in the pancreas yields acetaldehyde that is toxic to acinar cells. Acetaldehyde toxicity may be direct or stem from the production of reactive oxygen species generated during metabolism that results in oxidative stress in the pancreas (Majumdar et al. 1986; Nordback et al. 1991; Altomare et al. 1996). Alternative byproducts of non-oxidative ethanol metabolism, particularly fatty acid ethyl esters (FAEE) also have deleterious effects on the pancreas. Indeed, FAEE causes pancreatic edema, acinar vacuolization and trypsinogen activation when infused in rats (Criddle et al. 2004; Criddle et al. 2006). Recent reports have suggested that alcohol may increase the inflammatory response to an episode of pancreatitis by augmenting NF-κB translocation following activation of protein kinase C (Satoh et al. 2006). Although the precise mechanism of alcohol-induced pancreatitis is still under debate, current evidence supports a model in which metabolic byproducts of ethanol metabolism either cause direct injury to pancreatic acinar cells or sensitize these cells to injury by other toxic agents.

1.2.2.2 Hypertriglyceridemia

Elevated triglycerides (>1000 mg/dl) is a well established cause of acute pancreatitis. Patients with familial type V hyperlipoproteinemia develop hypertriglyceridemia and have an increased risk of pancreatitis. Other situations that can lead to dramatic elevations in triglyceride levels occur in pregnancy, oral contraceptive use (particularly in the setting of obesity, diabetes, or pre-existing hyperlipidemia), and vitamin A treatment. Women are particularly vulnerable to developing hypertriglyceridemia-induced pancreatitis in the third trimester of pregnancy when triglyceride levels typically increase three-fold. This is clinically relevant as there is a 10%–20% mortality rate for the fetus during an attack of acute pancreatitis in the third trimester (Ramin and Ramsey 2001).

The mechanism of hypertriglyceridemia-induced pancreatitis remains under investigation. Under normal conditions, triglycerides are hydrolyzed to free fatty acids by lipase expressed on endothelial cells. These free fatty acids are normally safely conveyed to the liver by lipoproteins and albumin. One model to explain the pathogenesis of triglyceride-induced pancreatitis is that in the context of elevated triglycerides, available albumin is saturated, and pancreatic capillaries are exposed to highly cytotoxic concentrations of circulating free fatty acids that can cause vascular endothelial damage, ischemic injury and inflammation (Sakorafas and Tsiotou 2000). Genetically engineered mice that mimic hyperlipidemic conditions in humans support this model and will be useful to further elucidate the mechanisms underlying hyperlipidemia-induced pancreatitis (Wang et al. 2008).

Diagnosing hyperlipidemic pancreatitis is a challenge because patients with abdominal pain and hypertriglyceridemia often do not have elevated amylase or lipase levels, as elevated circulating lipids block the chemical determination of amylase resulting in false negative test results. Urinary amylase testing is still accurate in these patients. The treatment is to decrease TG level to <500 mg/dl. Oral pancreatic enzymes are used to decrease pancreatic stimulation and decrease abdominal pain until triglyceride levels are stabilized. The diet should then consist of polyunsaturated fat, starch and fiber (instead of sucrose) (Toskes 1990).

1.2.2.3 Hypercalcemia

The association between acute pancreatitis and hypercalcemia has long been recognized. The most common underlying cause of hypercalcemia is hyperparathyroidism; however, only 1.5% of these patients develop acute pancreatitis, suggesting that other factors are required to develop pancreatitis in the context of hypercalcemia (Bess et al. 1980). Hypercalcemia associated with malignancy has also been shown to increase the risk of acute pancreatitis (Goldberg and Herschmann 1976). One mechanism that has been proposed for calcium-induced pancreatitis is that high levels of circulating calcium result in elevated intra-cellular calcium. Research has demonstrated that elevated cytosolic calcium can facilitate premature activation of zymogen granules within the acinar cell and cause injury or death to the cell injury. More detailed information regarding the role of calcium in the induction of pancreatitis will be discussed in Sect. 1.3.