Timothy B. Gardner
Kerrington D. Smith *Editors*

Pancreatology

A Clinical Casebook

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Preface

The field of clinical pancreatology has been transformed in the last several years by many notable developments in almost all aspects of care. The discovery and application of genetic markers has revolutionized the diagnosis of pancreatitis and helped to better define prognosis and treatment options. Minimally invasive endoscopic and surgical techniques have allowed patients to undergo complex procedures with faster recoveries. The development of total pancreatectomy with islet cell transplant has revolutionized therapy of benign pancreatic disease and offered hope to many patients previously thought to be incurable. As with other complex disease processes, the optimal care of the patient requires a dedicated team approach.

This clinical casebook provides a comprehensive, state-of the-art review and will serve as a valuable resource for clinicians, surgeons, researchers, and technology companies interested in caring for patients with pancreatic disease. It is focused on the diagnosis and early detection of pancreatitis and pancreatic cancer, including new developments in the field of genetics. Updates in the management of acute pancreatitis in the hospitalized patients are addressed. The treatment of complications from acute pancreatitis, especially focusing on new randomized trial data comparing minimally invasive endoscopic vs surgical techniques, is highlighted. The role and controversy of neoadjuvant therapy for pancreatic cancer is illustrated. Finally, the emerging treatment algorithms for chronic pancreatitis, including total pancreatectomy with islet autotransplant, are featured.

This textbook will serve as a very useful resource for physicians and researchers interested in all aspects of pancreatology. Its concise, yet comprehensive, case-based format summarizes the current data in the field and also serves as a clinical resource. From a research perspective, new areas for investigation and discovery are highlighted.

We would like to acknowledge the authors for their work in putting together their collective experiences, observations, and interpretation of the clinical controversies and treatment options available to patients suffering from pancreas disorders.

Lebanon, USA — Timothy B. Gardner
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Chapter 1
Risk Factors for Acute and Chronic Pancreatitis

Kartik Sampath and Timothy B. Gardner

Case Study

A 57-year-old female presented to the emergency room (ER) with 1 day of severe midepigastric pain radiating to the back. In the ER, she intimated severe nausea and had a witnessed non-bloody emesis episode. The patient was given intravenous hydration, ondansetron, and hydromorphone, which partially improved her symptoms.

Her past medical history was pertinent for gastroesophageal reflux disease (GERD) and ulcerative colitis (UC). Her UC was diagnosed 5 years ago, with a colonoscopy noting moderate pancolitis. Azathioprine (100 mg daily) was initiated and she has since been in clinical remission. This patient had no surgical history and denied any history of

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substance abuse (alcohol, tobacco, or illicit drug use). There was no family history of pancreatitis or gastrointestinal-based malignancy.

Her physical exam was notable for mild tachycardia with a normal temperature and oxygen saturation. She was noted to be in mild distress and anicteric and have slightly dry mucous membranes with normal breath sounds. Her abdomen was tender in the midepigastrium. Labs were notable for a white blood cell (WBC) count of 14,300, hematocrit of 46%, BUN of 27 mg/dL, and a creatinine of 0.97 mg/dL. Liver tests were within normal limits and a lipase was noted at 740 unit/L (upper limit of normal was 60 unit/L). CT scan (see Fig. 1.1) demonstrated interstitial pancreatitis.

My Management

A. She likely does not need a CT scan given the diagnosis is not in doubt.
B. The fact that her lipase is greater than three times the upper limit of normal in the context of appropriate clinical symptoms solidifies the diagnosis of acute pancreatitis.
C. We need to proceed with trying to determine the etiology for the episode of acute pancreatitis in order to prevent another attack from occurring.

Diagnosis and Assessment

AP is one of the most common reasons for gastrointestinal-based hospitalization [1]. Based on the 2012 revised Atlanta criteria, acute pancreatitis is defined by three factors: midepigastric pain radiating to the back, lipase elevation (three times the upper limit of normal), and a CT scan revealing evidence of AP [2]. To meet the criteria for diagnosis, two of the three criteria must be met. A CT scan can be normal early in the course of AP and is typically not ordered during the time of initial admission. In this particular case, the diagnosis is attained by the pain character and significant lipase elevation.

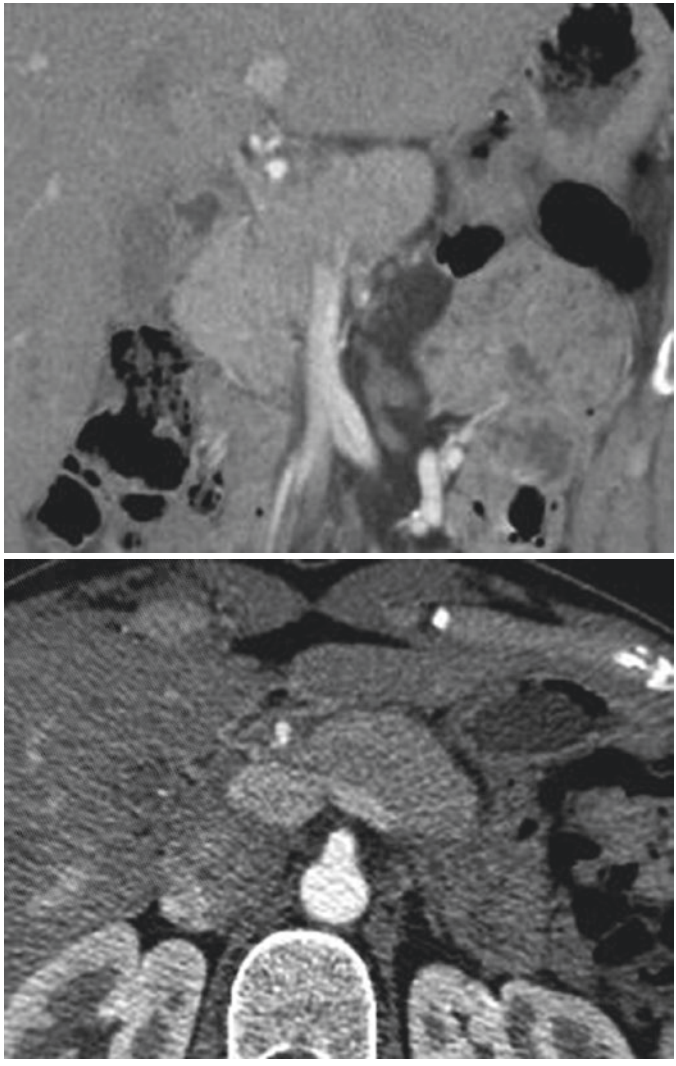

FIGURE 1.1 CT imaging of the pancreas revealed evidence of interstitial pancreatitis. In this case the pancreas was well perfused, edematous, without evidence of biliary or pancreatic duct dilation. Pancreatitis findings can also include indistinct pancreatic margins, peripancreatic fat stranding, and pancreatic hypoperfusion concerning for necrosis

Etiologies of Acute Pancreatitis

The most common cause of acute pancreatitis is gallstone pancreatitis (GP), which represents 45% of cases [3]. There are three types of gallstones: black, brown, and yellow stones. Black stones are related to active hemolysis. Brown stones are the sequelae of chronic biliary-based infections often in the setting of biliary obstruction. Yellow cholesterol stones are the most common; risk factors include female sex, pregnancy, obesity, physical inactivity, and overnutrition [4]. GP presentation typically includes cholestatic liver tests. An alanine aminotransferase (ALT) enzyme elevation three times the upper limit of normal in the setting of AP is associated with a positive predictive value of 95% for GP. A subset of GP is microlithiasis-induced pancreatitis. In these cases, cholestatic liver tests are noted; however abdominal imaging does not reveal evidence of biliary obstruction or gallstones. EUS can be useful in diagnosing subtle pancreatobiliary-based sludge. The management of biliary pancreatitis is discussed at length in a separate chapter.

Alcoholic pancreatitis accounts for an estimated 30% of cases. Interestingly, only 5–10% of chronic alcoholics develop acute pancreatitis [5]. Following AP management, alcohol cessation is recommended. In patients with continued alcohol abuse, there is an increased risk for RAP. Other less common causes of toxin-induced pancreatitis include methanol, organophosphate exposure, and scorpion venom.

Idiopathic pancreatitis (IP), where no definitive etiology can be ascertained, occurs in an estimated 15–25% of AP cases. IP is considered when an extensive negative workup has occurred which often includes serological workup, CT, MRCP, and/or EUS studies. It should be noted that smoking represents an independent risk factor for acute pancreatitis [6].

Hypertriglyceridemia pancreatitis (HTGP) represents 3% of AP cases and often can lead to RAP. HTGP can be genetic or acquired [7]. Familial hypertriglyceridemia increases the risk for AP and therefore family history represents a potential

risk factor. Acquired HTG occurs in the context of diabetes mellitus (DM), hypothyroidism, pregnancy, nephrotic syndrome, steroid use, beta-blockers, and tamoxifen use. Typically triglyceride levels over 1000 mg/dL significantly increase the risk for HTGP. Management includes aggressive hydration, analgesia, and IV insulin with IV dextrose. Plasmapheresis filters and effectively removes triglycerides. It is often reserved for TG levels greater than 1000 mg/dL with evidence of hypocalcemia and/or end-organ damage. Long-term management includes the use of fibrates, as well as optimizing predisposing comorbidities such as diabetes or hypothyroidism. Given that predisposing conditions such as DM or familial HTG can be difficult to control, HTGP patients often have an increased risk for RAP and severe pancreatitis-related morbidity.

Hypercalcemia is associated with acute pancreatitis in 1.5% of cases. Excess calcium is thought to promote pancreatitis via calcium-mediated activation of trypsinogen and pancreatic duct (PD) calcification deposition. Risk factors include hyperparathyroidism, malignancy, and numerous alternative etiologies of chronic hypercalcemia. Initial management includes IV hydration and treatment of the underlying etiology.

Medication-induced pancreatitis represents an estimated 1–2.5% of AP cases. Medication-induced pancreatitis literature ranges from case reports to larger observational studies to medication rechallenge trials [8]. The commonly associated drugs include azathioprine, estrogen, 5-ASA, sulfasalazine, metronidazole, pentamidine, didanosine, L-asparaginase, valproic acid, sulindac, salicylates, hydrochlorothiazide, and furosemide. The key management strategy is cessation of the offending medication and monitoring for RAP.

Due to extensive genetics research, hereditary pancreatitis (HP) is an increasingly diagnosed cause of RAP [9]. PRSS1 is a gain of function serine protease mutation that leads to autosomal dominant inheritance. The serine protease inhibitor Kazal type 1 (SPINK1) mutation leads to increased pancreatitis susceptibility. Mutation of the CFTR gene also leads to

HP via an autosomal recessive inheritance pattern. Key clinical risk factors include a family history of pancreatitis, presentation of RAP, and/or young age of initial presentation. HP is important to diagnose early on due to the increased risk for developing chronic pancreatitis and pancreatic cancer.

Acquired structural and congenital pancreatic abnormalities can increase the risk for AP. Pancreatic malignancy and pancreatic cysts such as main duct intraductal papillary mucinous neoplasms (IPMNs) can obstruct the pancreatic duct and lead to AP. Management involves surgical resection depending on lesion location and/or malignancy staging. Pancreatic divisum is estimated to arise in 10% of the general population [10]. RAP is noted in a subset of 8–10% of these patients. Minor duct papillotomy can be performed in these patients to facilitate pancreatitis duct drainage.

Autoimmune pancreatitis (AIP) is a rare but increasingly diagnosed cause of RAP. Keys to the diagnosis include the HISORt criteria: histology, imaging (inflamed pancreas without pancreatic duct dilation), serology (IgG4), other organ involvement, and response to steroid therapy [11]. AIP can be further substratified into type I and type II AIP. Type II AIP is associated with other autoimmune conditions such as inflammatory bowel disease (IBD). AIP diagnostic workup and management is discussed at length in a separate chapter.

Iatrogenic pancreatitis occurs post-ERCP or postsurgery. Post-ERCP pancreatitis occurs in 5% of patients; risk factors include performing an ERCP on patients with normal liver tests or a nondilated common bile duct [12]. Procedural-based risks include repeated pancreatic duct cannulation and contrast injection into the pancreatic duct. Postsurgical pancreatitis occurs due to blunt pancreatic trauma or injury during operative intervention. Management depends on the nature of the injury; however in cases where PD disruption is noted, pancreatic duct stenting may be of benefit.

Infections can lead to the development of AP, especially in children [13]. Viral infections associated with pancreatitis include mumps, coxsackie, hepatitis B, cytomegalovirus,

varicella zoster, herpes zoster, and human immunodeficiency virus. Predisposing bacterial infections include mycoplasma, legionella, leptospirosis, and salmonella. Fungal infections include aspergillosis and parasite-based infections include toxoplasmosis, cryptosporidium, and ascaris. Management consists of infection identification and subsequent treatment.

Peripancreatic vascular insufficiencies can lead to ischemia-induced pancreatitis. Global hypoperfusion states, atherosclerosis to peripancreatic arteries, and systemic vasculitis conditions such as lupus or polyarteritis nodosa can lead to pancreatitis. Management involves hydration and treatment of the underlying vascular-based disease process.

Other less common AP causes include trauma, pregnancy, post-renal transplantation, and alpha-1 antitrypsin deficiency. As prefaced above, the key is identifying and managing modifiable risk factors of AP in order to prevent progression to severe AP or RAP.

Etiology of Chronic Pancreatitis

CP represents the progression of chronic pancreatic inflammation to irreversible fibrosis. CP can present with chronic abdominal pain with or without pancreatic endocrine and exocrine dysfunction [14]. Typically there is evidence of CP on imaging (abdominal X-ray, CT, MRCP, and EUS) along with evidence of pancreatitis pain, diabetes, and/or fat malabsorption. The extensive diagnostic workup for CP is discussed at length in a separate chapter.

The most common cause of CP is alcohol abuse, where alcoholic chronic pancreatitis represents 50–70% of chronic pancreatitis cases. Idiopathic CP represents the next most common etiology, where despite extensive workup, no underlying cause has been determined. Smoking is an independent risk factor for CP. Hereditary pancreatitis has been increasingly identified in the previously diagnosed idiopathic chronic pancreatitis population. Structural and congenital pancreatic abnormalities can lead to PD reflux and the development

of CP. Risk factors include pancreatic pseudocysts, retained pancreatic duct stents, trauma, pancreatic duct stones, tumors, and pancreatic divisum.

Less common CP etiologies include HTGP, systemic vasculitis conditions, hyperparathyroidism, and autoimmune pancreatitis. Tropical pancreatitis has been described in the Southeast Asian population; however the exact pathogenesis is unclear and supportive care is generally advised.

Outcome

For the case study patient, an abdominal ultrasound was ordered which revealed no evidence of cholelithiasis, biliary dilation, or choledocholithiasis. The patient was treated with aggressive IV hydration. Subsequent hemoglobin A1c, lipid profile, and IgG4 labs were normal. An MRCP revealed no common bile duct or pancreatic duct abnormalities. Given the extensive targeted negative workup, it was suspected that the azathioprine was responsible for the AP presentation. This medication was discontinued and the patient was subsequently placed on infliximab. In follow-up, the patient was clinically doing well with no evidence of RAP.

Clinical Pearl/Pitfalls

- Acute pancreatitis diagnosis requires two of the following three criteria: epigastric abdominal pain radiating to the back, lipase elevation (three times the upper limit of normal), and CT findings consistent with AP.
- Alcohol and gallstone disease represent the most common etiologies of acute pancreatitis.
- Toxin-/medication-induced pancreatitis necessitates the removal of the toxic agent.
- Hypertriglyceridemia pancreatitis often occurs in the context of diabetes, hypothyroidism, or famil-

ial hypertriglyceridemia and is managed with IV hydration and IV insulin. Plasmapheresis is reserved for severe HTGP with evidence of end-organ dysfunction.
- Idiopathic pancreatitis is the third most common etiology of acute pancreatitis.
- Hereditary pancreatitis is associated with the PRSS1, SPINK1, and CFTR mutations and can often present with recurrent acute pancreatitis.
- Autoimmune pancreatitis is diagnosed with the HISORt criteria and can be associated with other autoimmune disorders.
- Chronic pancreatitis diagnosis consists of abnormal pancreatic imaging coupled with pancreatitis-type abdominal pain and/or pancreatic insufficiency.
- Alcohol is the most common cause of chronic pancreatitis.

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