Timothy B. Gardner
Kerrington D. Smith *Editors*

Pancreatology

A Clinical Casebook

Springer

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Editors
Timothy B. Gardner
Section of Gastroenterology
and Hepatology
Dartmouth-Hitchcock
Medical Center
Lebanon, New Hampshire
USA

Kerrington D. Smith
Department of Surgery
Dartmouth-Hitchcock
Medical Center
Lebanon, New Hampshire
USA

ISBN 978-3-319-53090-1 ISBN 978-3-319-53091-8 (eBook)
DOI 10.1007/978-3-319-53091-8

Library of Congress Control Number: 2017940242

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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
Lebanon, USA — Kerrington D. Smith

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Contributors

Jeffrey M. Adler, MD Section of Gastroenterology, Lebanon, NH, USA

Haaris A. Beg Internal Medicine, NYU Langone, New York, NY, USA

Gordon P. Bensen Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Katerina L. Byanova, MD Department of Internal Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Amelia M. Cullinan, MD Assistant Professor of Medicine, Geisel School of Medicine, Director, Outpatient Palliative Care Services, Section of Palliative Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Jason D. Ferreira, MD University Gastroenterology, Providence, RI, USA

Timothy B. Gardner, MD Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Maureen V. Hill, MD Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Nigeen H. Janisch, MD Department of Gastroenterology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Samuel J. Kesseli, BS Geisel School of Medicine at Dartmouth, Hanover, NH, USA

John M. Levenick, MD Department of Gastroenterology and Hepatology, Penn State, Milton S. Hershey Medical Center, Hershey, PA, USA

Raphael Louie, MD, MPH Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Anuradha Madhavan Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Jeannine B. Mills, MS, RDN, CSO, LD Gastrointestinal Cancer Group, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Kartik Sampath, MD Department of Gastroenterology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Kerrington D. Smith, MD Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Lisa Yoo, DO Department of Gastroenterology and Hepatology, Penn State, Milton S. Hershey Medical Center, Hershey, PA, USA

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

K. Sampath, MD (✉)
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Kartik.Sampath@Dartmouth.edu

T.B. Gardner, MD
Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.b.gardner@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_1,

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.

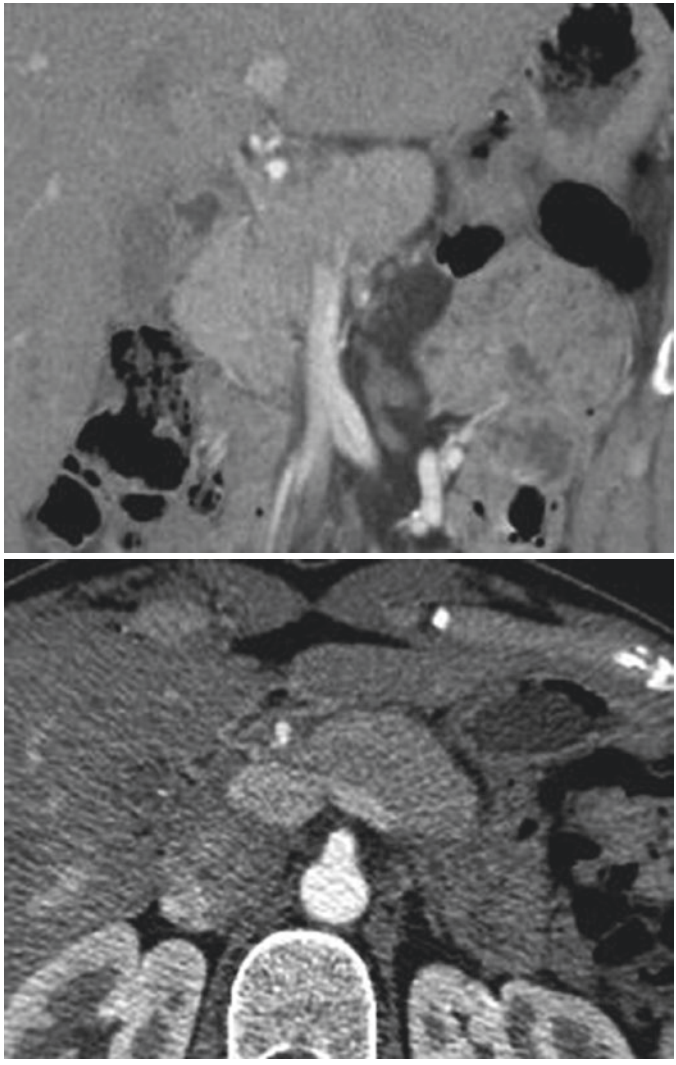

FIGURE 1.1 CT imaging of the pancreas revealed evidence of interstitial pancreatitis. In this case the pancreas was well perfused, edematous, without evidence of biliary or pancreatic duct dilation. Pancreatitis findings can also include indistinct pancreatic margins, peripancreatic fat stranding, and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

References

1. Dick 3rd JF, Gardner TB, Merrens EJ. Acute pancreatitis: new developments and strategies for the hospitalist. J Hosp Med. 2016;11(10):724–9.
2. Banks PA, Bollen TL, Dervenis C, et al. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11.
3. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1252–61.
4. Lammert F, Gurusamy K, Ko CW, et al. Gallstones. Nat Rev Dis Primers. 2016;2:16024.
5. Yang AL, Vadhavkar S, Singh G. Epidemiology of alcohol-related liver and pancreatic disease in the United States. Arch Intern Med. 2008;168(6):649–56.
6. Majumder S, Gierisch JM, Bastian LA. The association of smoking and acute pancreatitis: a systematic review and meta-analysis. Pancreas. 2015;44(4):540–6.

7. Vipperla K, Somerville C, Furlan A, et al. Clinical profile and natural course in a large cohort of patients with hypertriglyceridemia and pancreatitis. J Clin Gastroenterol. 2017;51(1):77–85.
8. Tenner S. Drug induced acute pancreatitis: does it exist? World J Gastroenterol. 2014;20(44):16529–34.
9. Solomon S, Whitcomb DC. Genetics of pancreatitis: an update for clinicians and genetic counselors. Curr Gastroenterol Rep. 2012;14(2):112–7.
10. Attwell A, Borak G, Hawes R, et al. Endoscopic pancreatic sphincterotomy for pancreas divisum by using a needle-knife or standard pull-type technique: safety and reintervention rates. Gastrointest Endosc. 2006;64(5):705–11.
11. Chari ST, Takahashi N, Levy MJ, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009;7(10):1097–103.
12. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366(15):1414–22.
13. Parenti DM, Steinberg W, Kang P. Infectious causes of acute pancreatitis. Pancreas. 1996;13(4):356–71. Review
14. Wilcox CM, Sandhu BS, Singh V, et al. Racial differences in the clinical profile, causes, and outcome of chronic pancreatitis. Am J Gastroenterol. 2016;111(10):1488–96.

Chapter 2
Hereditary Pancreatitis

Gordon P. Bensen and Timothy B. Gardner

Case Study

A 29-year-old female presents for evaluation of three episodes of acute pancreatitis in the context of having cystic fibrosis (CF). She was diagnosed at age 16 with CF due to recurrent pneumonias, sinus disease, and respiratory ailments. She is heterozygous for the E60X and AY55E mutations in the CFTR gene. On average she is admitted to the hospital 1–2 times per year for CF flares due to her lung dysfunction. One year ago she had a fecal elastase performed showing she was pancreatic sufficient.

The woman reports having three discreet episodes of acute pancreatitis where she was hospitalized for up to a week in all three instances. In each case she had considerable amounts of abdominal pain and recorded lipase values over 1500. She claims to feel fine in between episodes.

Her past medical history includes cystic fibrosis, Chiari malformation, mild depression, status post ventral hernia repair times two, status post lung embolization, and status post cholecystectomy. She reports no family history of pancreatic disease or

G.P. Bensen • T.B. Gardner, MD, MS (✉)
Section of Gastroenterology and Hepatology,
Dartmouth-Hitchcock Medical Center,
One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.b.gardner@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_2,

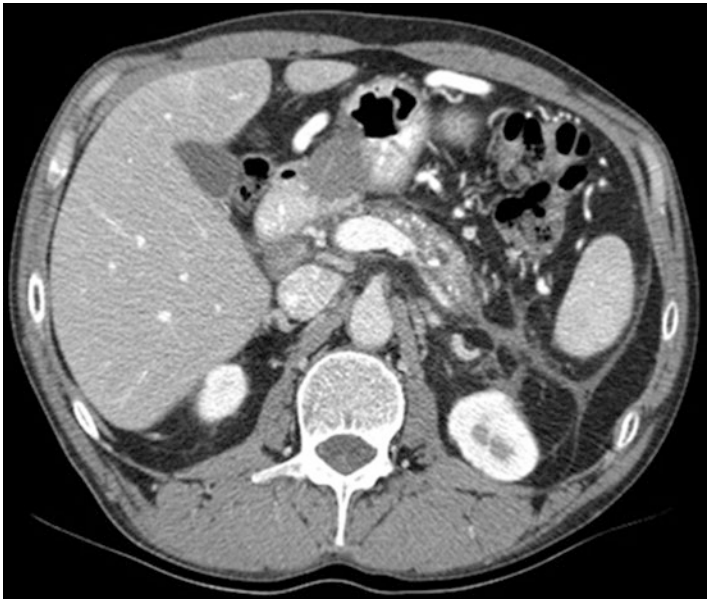

FIGURE 2.1 Representative CT scan from a patient with CFTR-induced pancreatitis. Note extensive calcifications, atrophy, and dilated main pancreatic duct

of CF. Two CT scans within the past year show and a cholecystectomy a few months ago ruled out biliary disease as a cause of her pancreatitis. She does however have extensive calcifications and pancreatic atrophy (Fig. 2.1). Her triglyceride and calcium levels are normal and she does not drink alcohol nor does she smoke.

My Management

1. Consider other causes of acute pancreatitis that could be also contributing to her disease such as pancreas divisum.
2. Evaluate for other concomitant problems related to CF such as fat-soluble vitamin deficiency.
3. If she has not been referred to a designated cystic fibrosis center, she should be referred at this time.

Diagnosis and Assessment

Hereditary pancreatitis is defined as chronic or recurrent acute pancreatitis that occurs as a result of abnormalities of specific pancreatitis-causing genes [1, 2]. Hereditary pancreatitis has three different inheritance patterns: autosomal dominant hereditary pancreatitis, autosomal recessive pancreatitis, and complex genetics. Autosomal dominant hereditary pancreatitis usually derives from a mutation in the PRSS1 (serine protease 1) gene. Autosomal recessive pancreatitis is most commonly from chronic pancreatitis associated with cystic fibrosis; however an autosomal recessive pattern can also emerge due to a mutation in the SPINK1 (serine protease inhibitor Kazal type 1) gene. Finally, multiple family members can face recurrent acute or chronic pancreatitis due to a combination of genetic and environmental factors—most commonly seen through patients with heterozygous SPINK1 mutations. No matter what the inheritance pattern, the basis of hereditary pancreatitis lies in having a specific disease-causing gene mutation.

There are many different gene mutations that can result in hereditary pancreatitis. Eighty percent of patients with hereditary pancreatitis have mutations in their PRSS1 gene. This gene codes for trypsin-1 (cationic trypsinogen). Mutations in the PRSS1 gene lead to malfunctioning trypsin-1 in which intracellular trypsinogen is converted to trypsin too early while still within the pancreas. Premature activation of trypsinogen then causes pancreatitis. The defense mechanism which allows for the premature activation is inhibited by mutations in the PRSS1 gene and in genes that encode molecules that protect the pancreas from active trypsin (these include SPINK1, CTRC, and CFTR).

The most common mutations in the PRSS1 gene include point mutations at the p. R122H and p. N291 loci—both of which have high penetrance. More than 20 PRSS1 mutations are known with new ones routinely being discovered. Nearly all mutations are associated with one of trypsin's two regulatory sites.

The SPINK1 gene is expressed in pancreatic acinar cells during an inflammatory process in which it inhibits trypsin secretion from the pancreas. Many people have a SPINK1 mutation; however <1% of carriers develop pancreatitis. The majority of patients with a SPINK1 mutation are heterozygous for that mutation. SPINK1 is only required by the body to work correctly when there is recurrent trypsin activation, and thus it most likely acts as a disease modifier where it lowers the threshold for developing pancreatitis due to other genetic or environmental factors. If some environmental or genetic incident causes the amount of trypsin activation to spike, SPINK1 would act as the feedback inhibitor that would perform the protective duty required to combat the trypsin. If the SPINK1 gene is mutated, this response won't occur, the pancreas won't be protected from activated trypsinogen, and pancreatitis may result.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene is the most common gene that is coupled with SPINK1 resulting in hereditary pancreatitis [3–6]. The CFTR gene encodes for proteins that create channels for sodium and bicarbonate. These cross-membrane channels create gradients for cell-produced material to move freely in and out of adjacent cells. These channels are needed in cells that create mucus, sweat, saliva, tears, and digestive enzymes. Properly functioning chloride channels are incredibly important for many organs and tissues as they allow for the production of thin and free-flowing mucus to protect the walls of the respiratory system, digestive tract, reproductive system, etc. The channels also ensure the proper secretion/activation rate of pancreatic enzymes that help digest foods by lining the pancreatic duct walls. Mutations in the CFTR gene (located on chromosome 7) result in cystic fibrosis (CF). CF mostly affects the lungs but also has the potential to damage the pancreas, liver, and vas deferens. The mutated CFTR causes the channels to malfunction resulting in a thick (instead of thin) mucus layer to line the duct walls, which in turn obstructs the minor duct and doesn't allow for proper secretion. This in turn

causes premature activation of pancreatic enzymes within the acinar cell which leads to pancreatitis.

CFTR mutations can cause pancreatitis whether or not the patient has other manifestations of cystic fibrosis. There are over 2000 mutations of the CFTR gene that can lead to malfunction. There are four main patterns seen in the relationship between CFTR mutation and pancreatitis:

1. *Homozygote or compound heterozygote for two acute CFTR mutations*. In this case, the CFTR protein is completely nonfunctioning. The patient shows classic symptoms of cystic fibrosis and usually acquires pancreatic insufficiency at an early age. Sometimes, these patients are pancreatic sufficient early in life and then are at risk for development of acute pancreatitis. CF patients who are pancreatic sufficient are the CF patients at risk for acute pancreatitis.
2. *Homozygote or compound heterozygote for a CFTR mutation where at least one of the gene copies has a moderate variant*. In this case, the CFTR protein retains part of its function. The patient shows signs of mild cystic fibrosis. Acute pancreatitis is very likely. The CFTR R75Q mutation is the most common example of this.
3. *CFTR variants that cause selective deficiency in bicarbonate conductance, labeled CFTR-BD*. In this case, patients have a very high risk of recurrent acute and chronic pancreatitis along with male infertility and chronic sinusitis. These patients, however, have no lung disease.
4. *Heterozygote for CFTR mutation*. In this case, patients show an increased risk of three- to fourfold for developing chronic pancreatitis when compared to the general population; however, 99% of these patients are healthy. Patients who do not develop chronic pancreatitis most often have a coexisting SPINK1 or chymotrypsin C (CTRC—see below) mutations leading to the conclusion that these genes are undergoing epistasis. These patients may have a higher risk of pancreatitis if they also have pancreatic divisum.

Three more gene mutations that can lead to hereditary pancreatitis include chymotrypsin C (CTRC), claudin-2 (CLDN2), and carboxypeptidase A1 (CPA1). Mutations in the CTRC gene convey a mild risk for pancreatitis—usually manifestations only appear with the presence of a mutation in the CFTR or SPINK1 gene as well. Chymotrypsin C is a digestive enzyme that communicates with activated trypsin. Some rare mutations cause chronic pancreatitis in children, while the most common mutation—G60G—causes chronic pancreatitis in adults. CLDN2 and CPA1 mutations are associated with recurrent acute and chronic pancreatitis. CLDN2 mutations may cause alcoholic chronic pancreatitis in alcohol-abusing patients. The gene lies on the X chromosome and thus the risk for men is dominant. Carboxypeptidase A1 is the second most abundant enzyme in pancreatic juice after trypsinogen. Mutations in the CPA1 gene lead to nonalcoholic chronic pancreatitis. The development of pancreatitis from a CPA1 mutation is not dependent on trypsin activity.

Our patient's episodes of acute pancreatitis undoubtedly come from her cystic fibrosis. She is heterozygous for two CFTR mutations (E60X and AY55E) that caused her CF. As described above, a heterozygote CFTR mutation carrier is one of the four main patterns seen between CFTR mutations and pancreatitis. It is also possible that she is actually compound heterozygous as she has symptoms of typical cystic fibrosis (sinus issues, lung issues, etc.) and pancreatic sufficiency which fall in line with the compound heterozygote CFTR mutation and pancreatitis pattern. Two or three of CF patients are pancreatic insufficient from birth and another 20–25% develop it early in life. Thus, most CF patients are pancreatic sufficient, leading to pancreatitis. Because our patient is pancreas sufficient, she developed pancreatitis later in life. As described above, she is in the minority of CF patients who are pancreatic sufficient in their childhood and are at risk for developing acute and chronic pancreatitis later in life [7].

Management

Most importantly, the patient must continue to avoid alcohol and tobacco as these toxins can contribute to progression of her pancreatitis symptoms. Her pancreatitis can also be exacerbated due to emotional stress and high intake of dietary fat. Our patient needs to make sure she continues to try and eat a healthy, low-fat diet. Referring the patient to a nutritionist may be beneficial. It may also be necessary to look into her source of depression to make sure that it is not stress related. From a genetic perspective, often times the CFTR mutation is not the only one at work. Genetic testing could be performed to determine if there may be a SPINK1 mutation that is contributing to the problem. Genetic testing is often done to look at the PRSS1, CFTR, SPINK1, and CTRC genes. Determining what other genes may or may not be involved will not change our management approach or her condition and risk stratify her for eventually developing a pancreatic malignancy.

In managing our patient's pancreatitis, the most important initial treatment is pain control. Next, the patient should have a CT scan and/or MRCP performed to look into the ductal anatomy of the pancreas and see if there is anything obstructive that could be treated endoscopically or surgically. We know that in the heterozygous CFTR/pancreatitis pattern, the CFTR mutations may only cause pancreatitis in the presence of pancreatic divisum. If the CT scan or MRCP shows evidence of obstruction of the minor duct, we may be able to fix the issue endoscopically with ERCP.

Outcome

Patients with hereditary pancreatitis have a very high risk of developing pancreatic cancer. Studies have shown that there is an overall 40–45% chance that patients with PRSS1 mutations will develop pancreatic adenocarcinoma by age 70. However, the likelihood changes depending on a number of

different factors such as age, smoking habits, and prevalence of diabetes. As the patient ages, the chance of developing pancreatic cancer increases significantly (one trial found that from ages 50–75, the likelihood increased from 10% to 54%). For nonsmokers, the chances of developing pancreatic cancer drop significantly to less than 20%, while the risk increases by approximately twofold for smoking patients. Furthermore, smoking patients with hereditary pancreatitis also develop pancreatic cancer an average of 20 years earlier than nonsmokers. Finally, hereditary pancreatitis patients with diabetes have a much higher chance of developing pancreatic cancer. Due to these risks, screening patients for pancreatic cancer has been advocated. Total pancreatectomy with autoislet transplant surgery is performed usually for pain management, although may be performed in this setting as a means of reducing the risk of developing pancreatic adenocarcinoma.

Clinical Pearls/Pitfalls

- Hereditary pancreatitis should be considered in younger patients with idiopathic pancreatitis or in any patient with a strong family history of pancreatitis and/or pancreatic cancer.
- Evaluating for hereditary pancreatitis is performed via readily available serum tests.
- PRSS1, SPINK1, and CFTR mutations are the most common genes implicated in hereditary pancreatitis.
- Patients with hereditary pancreatitis are at high risk for eventually developing pancreatic adenocarcinoma.

References

1. Dorfman R. Cystic fibrosis mutation database. In: Cystic fibrosis mutation database; 2011. http://www.genet.sickkids.on.ca/cftr/home.html. Accessed 17 Jun 2016.

2. Freedman SD. Treatment of chronic pancreatitis. In: UpToDate. http://www.uptodate.com/contents/treatment-of-chronic-pancreatitis?source=see_link; 2014. Accessed 17 Jun 2016.
3. CFTR. In: Genetics home reference. https://ghr.nlm.nih.gov/gene/cftr#conditions; 2016. Accessed 17 Jun 2016.
4. Katkin JP. Cystic fibrosis: genetics and pathogenesis. In: UpToDate. http://www.uptodate.com/contents/cystic-fibrosis-genetics-and-pathogenesis; 2014. Accessed 17 Jun 2016.
5. Katkin JP. Cystic fibrosis: clinical manifestations and diagnosis. In: UpToDate. http://www.uptodate.com/contents/cystic-fibrosis-clinical-manifestations-and-diagnosis; 2016. Accessed 17 Jun 2016.
6. Whitcomb DC. Cystic fibrosis. In: Pancreas.org: information and help about pancreatic diseases. https://pancreas.org/patients/cystic-fibrosis/; 2009. Accessed 17 Jun 2016.
7. Whitcomb DC. Hereditary pancreatitis. In: UpToDate. http://www.uptodate.com/contents/hereditary-pancreatitis; 2016. Accessed 17 Jun 2016.

Chapter 3
Hospital Management of Acute Pancreatitis

Nigeen H. Janisch

Case Study

A 56-year-old woman presents with a 10-year history of recurrent abdominal pain in her right upper quadrant with a cholecystectomy 5 years ago. Her previous workups revealed a mild transient transaminase elevation with a normal lipase and amylase. All subsequent imaging was unremarkable. During this presentation, AST and ALT were 304 and 280, respectively, and an ultrasound showed the common bile duct to be dilated at 10 mm. Patient history and clinical symptoms suggested a possible sphincter of Oddi dysfunction, so ERCP with sphincterotomy was scheduled for the next day. About 4 h post-procedure, the patient complained of continuous, severe epigastric pain radiating to the back along with intractable nausea and vomiting. Lipase at this time was 1500 and vital signs were stable. Diagnosis of post-ERCP acute pancreatitis was made, and the patient was admitted to an ICU step-down unit on intravenous lactated Ringer's at 250 ml/h.

N.H. Janisch, MD
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Nigeen.H.Janisch@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_3,

My Management

A. Agree with current management.
B. Continue aggressive fluid resuscitation at 250 ml/h.
C. Monitor BUN, Cr, and hematocrit at least every 12 h.
D. Attempt enteral feeding orally within 48 h.

Diagnosis and Assessment

The risk of post-ERCP pancreatitis after diagnostic ERCP is thought to be 0.4–1.5%, while therapeutic ERCP is 1.6–5.4%. However, some risk can be as high as 10–20% in certain demographics, including those undergoing ERCP for the evaluation of sphincter of Oddi dysfunction and those with a past history of post-ERCP pancreatitis [1]. Etiology of acute pancreatitis in patients receiving ERCP is usually due to instrumentation with specific attention given to difficult cannulation of the biliary tree and needle-knife sphincterotomy [2].

Diagnosis of acute pancreatitis has been established by the presence of two of the following three criteria: (1) abdominal pain, (2) serum amylase or lipase greater than three times the upper limit of normal, and (3) suggestive findings on imaging [3]. However, imaging is not required for diagnosis if clinical suspicion is high, and a CT scan may not even show signs of acute pancreatitis if done within 3 h of symptom onset. Once a patient is diagnosed, resuscitation should begin immediately based on the patient's hemodynamic status. Clinical evaluation should consider the need for admission to an ICU or step-down unit depending on the patient's course of disease and presence of organ failure signs. Our patient was correctly managed after diagnosis with immediate fluid resuscitation and placement into an intermediate care unit to increase the staff's ability for frequent reevaluation [3].

The revised Atlanta classification from 2013 divides acute pancreatitis into mild, moderately severe, and severe [4]. Mild pancreatitis, or interstitial edematous pancreatitis, features pancreatic inflammation without necrosis or organ failure

and usually resolves within 1 week without any further sequelae. Moderately severe pancreatitis requires the presence of local complications or transient organ failure that resolves by the 48 h mark. Severe pancreatitis, however, may result in pancreatic necrosis, abscess formation, and pseudocysts and is characterized by persistent organ failure lasting longer than 48 h [4]. With acute pancreatitis, timing, evaluation, and prompt treatment of the patient in the first 48 h after diagnosis are critical.

Predicting the severity of acute pancreatitis can be challenging. Laboratory abnormalities in hematocrit, creatinine, and blood urea nitrogen (BUN) have been studied as prognostic indicators [5–7]. The risk of pancreatic necrosis may increase with elevated hematocrit at admission or failure to decrease said value after 24 h [5]. Increased creatinine within 48 h of admission has also been implicated in poor outcomes [6]. Lastly, BUN ≥20 mg/dl at admission or a rise within the first 24 h poses a poor prognosis [7].

Management

With a diagnosis of acute pancreatitis following an ERCP procedure, the most important initial step is fluid resuscitation with two general rules—high volume and immediate initiation. Though our patient is presently hemodynamically stable, acute pancreatitis can cause an intense hypovolemia along with a devastating combination of microangiopathic effects and pancreatic edema that leads to pancreatic necrosis and ongoing pancreatic enzyme release. This patient's initial intravenous fluid rate of 250 ml/h is at the lower end of the ACG recommended spectrum of 250–500 ml/h [3]. Though an optimal rate has not been agreed upon, evidence does show a decreased morbidity and mortality with aggressive hydration in the first 24 h, while 48 h has no effect on patient outcome. For this patient, we would recommend continued close monitoring and reevaluation of the fluid rate every 6 h using a decreasing BUN and a urine output greater than 0.5 ml/kg as markers for improvement [8, 9].

Prognosis for patients such as this can be difficult to determine. While the lipase is paramount in diagnosis, it is not a good tool to trend for severity. Studies have suggested that decreases in hematocrit, creatinine, and BUN within the first 24 h are more accurate indicators of a good prognosis. While there are no numeric goals to decrease to, a BUN greater than 20 mg/dl at admission or a rise within the first 24 h has been linked to an increased risk of mortality and death [7].

In the past, this patient would have been kept NPO until pain resolution. However, bowel rest is now thought to be associated with intestinal mucosal atrophy and thus increased infectious complications via bacterial translocation. Therefore, enteral feeding is now recommended to start within the first 72 h of hospitalization with tube feeds as tolerated. Studies have shown benefits in mortality, infection, organ failure, and lower surgical rate in patients given enteral feeds compared to parenteral feeds [10]. We were able to use nasojejunal feeding in this patient after 48 h that was fairly well tolerated, though a nasogastric feed is similar in effect if better for the patient.

Pancreatic necrosis as a complication of acute pancreatitis is always a worry as it is responsible for up to 70% of all deaths, though only present in 5% of patients presenting with acute pancreatitis [11]. Previously, prophylactic antibiotic therapy was thought to be a reasonable solution to this serious infectious complication and has been heavily debated through the years. However, it is currently not recommended for the prevention of pancreatic necrosis. Antibiotic therapy should be strictly avoided in patients with acute pancreatitis and not administered within the first 24 h unless there is clinical suspicion for concurrent infection [3].

Outcome

This patient had an initial BUN of 12 mg/dl, with no history of renal disease, taken at the time of the original elevated lipase. The patient remained on 250 ml/h lactated Ringer's for

24 h with some mild respiratory desaturations to 88%, which was corrected with nasal cannula oxygen. The BUN after 24 h was 10 mg/dl with a reduction in abdominal pain and nausea. Enteral feeding was attempted at 48 h and tolerated well at slow rates and small volumes. The patient was eventually discharged 5 days post-ERCP with no signs of pancreatic necrosis or pseudocyst formation, though confirmation may be needed with imaging at a later date.

Clinical Pearls/Pitfalls

- Early aggressive fluid resuscitation with the use of an isotonic crystalloid fluid, lactated Ringer's, running at 250–500 ml/h is recommended within the first 24 h of admission.
- Fluid boluses of 1–2 l during initial evaluation may be helpful in those presenting with severe volume depletion.
- Fluid resuscitation end point goals are a urine output greater than 0.5 ml/kg and a decreasing hematocrit and BUN after 24 h.
- Total infusion within the first 24 h to be 2.5–4.0 l with reassessment of fluid requirements every 6 h.
- Etiology must be addressed, as some causes of acute pancreatitis are reversible.
- Antibiotics are not recommended for prophylaxis of necrotizing acute pancreatitis and should only be used for a documented infection.
- Enteric feeding may be attempted within the first 72 h of admission if tolerated and may be supplemented with an oral low-fat diet if needed.
- There are no currently targeted pharmacologic therapies indicated for the treatment of acute pancreatitis.
- For patients at high risk for post-ERCP pancreatitis, it is recommended to administer 100 mg rectal indomethacin for post-procedure prophylaxis.

References

1. Arata S, Takada T, Hirata K. Post-ERCP pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:70–8.
2. Masci E, Toti G, Mariani A. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol. 2001;96:417–23.
3. Tenner S, Baillie J, et al. American College of Gastroenterology Guideline: Management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400–15.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
5. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. Pancreas. 2000;20:367–72.
6. Muddana V, Whitcomb DC, Khalid A, et al. Elevated serum creatinine as a marker of pancreatic necrosis in acute pancreatitis. Am J Gastroenterol. 2009;104:164–70.
7. Wu BU, Bakker OJ, Papachristou GI, et al. Blood urea nitrogen in the early assessment of acute pancreatitis. Arch Intern Med. 2011;171:669–76.
8. Talukdar R, Vege SS. Early management of severe acute pancreatitis. Curr Gastroenterol Rep. 2011;13:123–30.
9. Besselink M, van Santvoort H, Freeman M, et al. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1–15.
10. Yi F, Ge L, Zhao J, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med. 2012;51:523–30.
11. Appelros S, Lindgren S, Borgström A. Short and long term outcome of severe acute pancreatitis. Eur J Surg. 2001;167:281–6.

Chapter 4
Acute Biliary Pancreatitis

Haaris A. Beg

Case Study

A 45-year-old woman came into the emergency department presenting with a 1-h history of sudden onset, severe epigastric pain radiating to the back. She reports having had a similar episode of abdominal pain after eating a fatty meal several months ago, but the pain was duller and resolved after a few hours. She has a past medical history significant only for hypertriglyceridemia. On presentation, serum amylase and lipase were 50 U/L and 100 U/L, respectively, but both had increased to >400 U/L when taken 6 h later. The patient continued to have persistent severe pain over the next 48 h, along with fever and nausea, despite aggressive hydration. Contrast-enhanced CT imaging (CECT) showed evidence of a stone in the distal common bile duct. With the possibility of severe acute pancreatitis and obstructing gallstone, the consulting gastroenterologist decided to admit the patient for an endoscopic retrograde cholangiopancreatography (ERCP) procedure.

H.A. Beg
Internal Medicine, NYU Langone,
545 1st Avenue Apt 4F, New York, NY 10016, USA
e-mail: haaris.beg@nyumc.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_4,

My Management

a. Agree with the consulting gastroenterologist to admit the patient for an ERCP.
b. Continue aggressive intravenous hydration for the next 24–72 h.

Diagnosis and Assessment

This is a patient who fulfills the diagnostic criteria for acute pancreatitis (AP) given both the history of sudden, severe pain radiating to the back and having elevated pancreatic enzymes, i.e., amylase and lipase. The most common causes of AP are gallstones (40–70%) and alcohol (25–35%). Due to the high prevalence of gallstones, which often cause recurrent disease, abdominal ultrasound should be performed on all patients presenting with AP. Ultrasound detects gallstones as small as 2 mm with a sensitivity >95% and can also rapidly be performed at the bedside [1]. If abdominal ultrasound is not performed upon presentation, it is important to get a thorough history.

Patients with acute biliary pancreatitis, or pancreatitis caused by gallstones, often have had episodes of biliary colic before presenting with AP. Biliary colic occurs when the gallbladder contracts against a cystic duct obstructed by a gallstone. Similar to this patient, biliary colic causes right upper quadrant pain that may radiate to the shoulder and often occurs after a fatty meal. The pain, however, often does not last beyond a few hours. There may be associated nausea and vomiting as well.

Identifying risk factors for developing gallstones is also important for diagnosis. These include age >40, female sex, family history, obesity, and certain ethnicities including Northern Europeans and Hispanics [2]. A simple pneumonic often used to remember the risk factors is “fat, forty, female, fertile, and fair.” Lab criteria for diagnosis require serum amylase and/or lipase greater than three times the upper limit of

normal. Serum amylase cannot be used alone for diagnosing AP, and serum lipase is preferred. It should be noted that both enzymes rise within a few hours after onset of symptoms. Additional tests that can help differentiate biliary pancreatitis from other causes of pancreatitis include the liver function tests. For example, a recent study has shown that the specificity of a serum ALT >150 IU/L for diagnosing gallstone pancreatitis was 96%, although the sensitivity is only about 50% [3].

Gallstones that cause biliary colic, or even full-blown AP, most often pass to the duodenum and are lost in stool. There is a minority of patients, however, that can have ongoing pancreatic duct and/or biliary tree obstruction due to having persistent gallstones. This can lead to severe AP, as occurred in our patient, and/or cholangitis, which is an infection of the biliary tract that often causes fever, jaundice, and right upper quadrant pain. The diagnosis of severe AP is made when patients fail to improve clinically within the first 48–72 h despite appropriate initial therapy, such as IV hydration [4]. Those that fail to improve often have persistent severe pain, fever, nausea, vomiting, or are unable to start oral feeding.

Although imaging beyond an ultrasound is usually not recommended when a patient initially presents with AP as most have a mild, uncomplicated course, this patient has not been getting better and has many risk factors for having a retained gallstone causing continued pancreatic inflammation and damage. In this setting, further investigation is required and CECT or MRI imaging is the next step. CECT imaging has a 90% sensitivity and specificity for diagnosing AP. Furthermore, it may help visualize bile duct stones, as it did in this patient, and also allows providers to assess the extent of pancreatic damage, which can help predict the severity of disease. The CT finding of CBD stones may have sensitivity as high as 80% [5]. MRI, on the hand, is better able to detect gallstones in the bile ducts down to 3 mm diameter by employing magnetic resonance cholangiopancreatography (MRCP). MRI is also more advantageous to use in patients with a contrast allergy and/or renal disease [6]. MRI, however, has a longer scanning time compared to the CT and is often difficult to perform in severely ill patients.

In conclusion, this patient, with a history of biliary colic and who has several risk factors for developing gallstones, already had a high probability of acute biliary pancreatitis. Ultimately, this was confirmed with imaging.

Management

The confirmation of a bile duct stone via imaging in a patient who has not been improving clinically over the last 48–72 h warrants an ERCP. If the stone was found on early initial imaging, it is most appropriate to treat conservatively in most patients who lack laboratory or clinical evidence of ongoing biliary obstruction, which includes bowel rest and intravenous fluid replacement before considering a more invasive intervention such as an ERCP. ERCP is a specialized technique used to study the bile ducts, pancreatic duct, and gallbladder. A physician passes an endoscope through the patient's mouth all the way into the duodenum until it reaches the point where the ducts from the pancreas and gallbladder drain into the duodenum. X-rays are subsequently taken. The endoscope allows for small tools to past through, enabling physicians to biopsy abnormal tissue, remove gallstones, open a narrowed bile duct, and even insert stents in the duct. Often times ERCPs necessitate the use of sphincterotomy, which involves cauterizing the sphincter of Oddi (a muscle that controls flow of pancreatic juices and biles into the duodenum) to further extract bile duct stones and facilitate the placement of stents. The procedure is not without complications, the most common of which is post-ERCP-induced pancreatitis, occurring at a rate of nearly 3–5% [7]. Other serious yet less common complications include perforation (esophagus, stomach, duodenum, or jejunum), bleeding, and sepsis.

An ERCP is strongly recommended for patients with both AP and concurrent acute cholangitis within 24 h of admission [8]. Our patient initially had a mild-moderate course and did not present with cholangitis so was managed

conservatively. She eventually began having worsening symptoms concerning for cholangitis and was therefore immediately taken for an ERCP. Studies have also found that patients with acute biliary pancreatitis with a severe predicted course had fewer complications, such as organ failure and/or necrosis, if they underwent early ERCP (within 72 h of admission). Mortality, however, was not significantly different between the two groups [9, 10]. Recent studies have also confirmed that early ERCP within 24 h of admission decreases morbidity and mortality in patients with AP complicated by biliary sepsis or infection that has spread to the bloodstream causing organ damage. The utility of early ERCP, however, continues to be studied with often conflicting results.

Importantly, if gallstones are found to be the cause of AP, the patient should immediately be referred for a cholecystectomy to prevent recurrent attacks and potential biliary sepsis [11]. This is also true of patients who have undergone endoscopic sphincterotomy [12]. In patients who have mild pancreatitis, cholecystectomy can be performed within 7 days after recovery and often times within the same hospitalization period after the patient gets better with conservative management [13, 14]. If a cholecystectomy is not performed in a patient with gallstone pancreatitis, there is a 25–30% risk of recurrent acute pancreatitis, cholecystitis, or cholangitis within 6–18 weeks [15]. To prevent these complications, it is imperative all patients with gallstone pancreatitis be referred for cholecystectomy after they recover.

Outcome

The patient was admitted for an ERCP, during which the gastroenterologist passed an endoscope to the duodenum, performed a sphincterotomy, and was successfully able to extract a 1 cm gallstone. The patient was monitored closely for the next 12 h after the procedure for signs of pancreatitis,

bleeding, perforation, or infection. Asymptomatic and hemodynamically stable, the patient was able to resume normal diet the following morning with follow-up amylase levels now decreased to <100 U/L. She was referred for cholecystectomy to be accomplished as an outpatient a few days after discharge.

Clinical Pearls/Pitfalls

- AP is most commonly caused by gallstones, which can be quickly and very accurately diagnosed via abdominal ultrasound at the bedside.
- Thorough history taking and identifying risk factors are crucial to diagnosis. Remember the pneumonic "fat, forty, female, fertile, and fair" as means to quickly identify those of high risk of developing gallstones.
- A low serum amylase and lipase level does not exclude pancreatitis, as these levels tend to rise hours after the onset of symptoms.
- Severe AP is diagnosed when patients fail to improve with IV hydration within 48–72 h, often having persistent pain and inability to tolerate diet by mouth.
- CT or MRI is recommended when patients fail to improve within 48–72 h, allowing providers to both visualize gallstones and evaluate extent of pancreatic damage. Of note, these tests are less sensitive at detecting stones than ultrasound.
- ERCP is a specialized endoscopic technique allowing gastroenterologists to remove gallstones utilizing special tools under fluorescent guidance.
- ERCP is warranted when a bile duct stone has not only been confirmed via imaging but also if a patient hasn't improved in 48–72 h with conservative therapy.
- ERCP is first-line treatment for any patient presenting with both AP and acute cholangitis within 24 h.

- Always monitor patients closely after ERCPs for complications, especially ERCP-induced pancreatitis which can occur nearly 3–5% of the time.
- The majority of patients are able to return to a normal diet the morning after an ERCP and are often discharged asymptomatic without complication.
- All patients found to have pancreatitis secondary to bile duct stones should be referred for cholecystectomy as they have a high risk of repeat pancreatitis, cholecystitis, and cholangitis.

References

1. Walton TJ, Dhingsa R, Kaye PV, Lobo DN. Imaging after medically managed severe acute cholecystitis. Gut. 2009;58(3): 421.. 472
2. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep. 2005;7(2):132–40.
3. Agarwal N, Pitchumoni CS, Sivaprasad AV. Evaluating tests for acute pancreatitis. Am J Gastroenterol. 1990;85:356–66.
4. Banks PA, Bollen TL, Derenis C, et al. Classification of acute pancreatitis-2012: revision of Atlanta classification and definitions by international consensus. Gut. 2012;62:102–11.
5. Baron RL, Stanley RJ, Lee JK, Koehler RE, Levitt RG. Computed tomographic features of biliary obstruction. AJR Am J Roentgenol. 1983;140(6):1173–8.
6. Stimac D, Milletic D, Radic M, et al. The role of non enhanced magnetic resonance imaging in the early assessment of acute pancreatitis. Am J Gastroenterol. 2007;102:997–1004.
7. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc. 1998;48(1):1.
8. Fan ST, Lai EC, Mok FP, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med. 1993;328 :228–32.

9. Neoptolemos JP, London NJ, James D, et al. Controlled trail of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative management for acute pancreatitis due to gallstones. Lancet. 1988;3:979–83.
10. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol. 2012;107:1096–103.
11. Moreau JA, Zinsmeister AR, Melton LJ, et al. Gallstone Pancreatitis and the effect of cholecystectomy. Mayo Clin Proc. 1988;63:466.
12. Laws HL, Kent 3rd RB. Acute pancreatitis: management of complicating infection. Am Surg. 2000;66(2):145.
13. Uhl W, Muller CA, Krahenbuhl L, Schmid SW, Scholzel S, Buchler MW. Acute gallstone pancreatitis: timing of laparascopic cholecystectomy in mild and severe disease. Surg Endosc. 1999;13(11):1070.
14. Aboulian A, Chan T, Yaghoubian A, Kaji AH, Putnam B, Neville A, Stabile BE, de Virgilio C. Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: a randomized prospective study. Ann Surg. 2010;251(4):615–9.
15. Hernandez V, Pascual I, Almela P, Anon R, Herreros B, Sanchiz V, Minguez M, Benages A. Recurrence of acute gallstone pancreatitis and relationship with cholecystectomy or endoscopic sphincterotomy. Am J Gastroenterol. 2004;99(12):2417.

Chapter 5
Classification and Management of Pancreatic Cysts

Katerina L. Byanova and Timothy B. Gardner

Case Study

A 65 year-old woman is referred to Gastroenterology for evaluation of a pancreatic cyst found incidentally on a non-contrast CT obtained 2 weeks prior. At the time the imaging was obtained, the patient had presented to the ED with classic symptoms of nephrolithiasis (flank pain, hematuria, nausea/vomiting), which have since resolved completely. CT obtained in the ED as part of the workup revealed a 3 cm cystic structure in the head of the pancreas. Due to limitations of the study, the size of the pancreatic duct and the cyst was not characterized further.

K.L. Byanova, MD (✉)
Department of Internal Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA
e-mail: kbyanova@bidmc.harvard.edu

T.B. Gardner, MD
Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.b.gardner@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_5,

The patient is anxious and surprised by the finding. She denies any history of pancreatitis or jaundice, as well as any recent infections or history of inflammatory disease. She has no relevant past medical history. She has never smoked cigarettes and also does not consume alcohol. There is no personal history of cancer, nor any family history of pancreatic or other cancers.

The patient undergoes MRI of the abdomen with contrast, which measures the cyst at 3.1 cm and the pancreatic duct at 5 mm. There is no wall enhancement, but a mural nodule is noted within the cyst.

My Management

A. *I will recommend an endoscopic ultrasound with fine needle aspiration.*
B. *I will refer to surgery.*

Diagnosis and Assessment

Pancreatic cysts are fluid-filled lesions of various etiologies. They are frequent incidental findings on imaging in asymptomatic patients, seen in 20% of all MRIs and 3% of all CTs of the abdomen. With the increasing use of higher resolution and more sophisticated imaging modalities, pancreatic cysts are now also diagnosed not only more frequently but also at a smaller size [1–3].

When a cyst is found, like in our patient, the first step is to differentiate between a pancreatic pseudocyst and a true cyst. A pseudocyst is a lesion without a true wall that usually forms in the context of acute pancreatitis and resolves over the course of several months [2]. A true pancreatic cyst is more likely if there is no history of pancreatitis, inflammation, recent infection or pancreatic disease [2].

If the clinical presentation suggests a true cyst, the next step is to determine the type of cyst, as each type confers

different risk of malignancy and thus a different prognosis. There are five types of cysts to be considered—mucinous cystic neoplasia (MCN), intraductal papillary mucinous neoplasia (IPMN: could be main duct, MD-IPMN, or branch duct, BD-IPMN), serous cystadenoma (SCA), solid pseudopapillary neoplasia (SPN), and cystic pancreatic neuroendocrine tumor (CPEN) [2]. These lesions can be differentiated at least partly based on patient characteristics, cyst localization, or associated symptoms; for example, a single lesion in a symptomatic female in her 20s or 30s strongly points to SPN, while a cyst in the head of the pancreas in an elderly man with symptoms of pancreatitis or obstructive jaundice raises the suspicion for a MD-IPMN [1, 2, 4]. A summary of the key characteristics of each type of cystic lesion and their malignant potential follows:

- Mucinous cystic neoplasia (MCN): Comprises a fourth of all resected pancreatic cysts. These cysts are commonly found in women in their 40s and may present with abdominal pain, jaundice, or pancreatitis. MCNs are notable for their ovarian stroma-like lining, lack of communication with the pancreatic duct, and mucin-containing fluid [2, 4]. Because of 20% risk of progression to malignancy, these cysts are typically resected [2, 4]. Long-term outcomes depend on whether the lesion was invasive at the time of surgery, with excellent 5-year survival if not malignant [2].
- IPMN: Altogether, IPMNs account for 38% of all resected pancreatic cysts [2]. These cysts occur as single or multiple lesions and are unique in their communication with the pancreatic duct. They are found equally in men and women, usually in their 60s. While some patients are asymptomatic, others, especially with MD-IPMN, will present with obstructive symptoms such as jaundice, pancreatitis, and abdominal pain [4].
  - MD-IPMN: Main-duct IPMNs carry a significantly higher risk of malignancy compared to BD-IPMN. These cysts classically cause recurrent pancreatitis and dilation

of the pancreatic duct, as well as changes in the morphology of the papilla ("fish-mouth" papilla) [4]. MD-IPMNs have a malignancy rate of over 60% and warrant a resection [4, 5]. Five-year survival is 95–100% if no evidence of invasion is found on resection, but only 40–60% if malignant [2]. See Figs. 5.1 and 5.2.

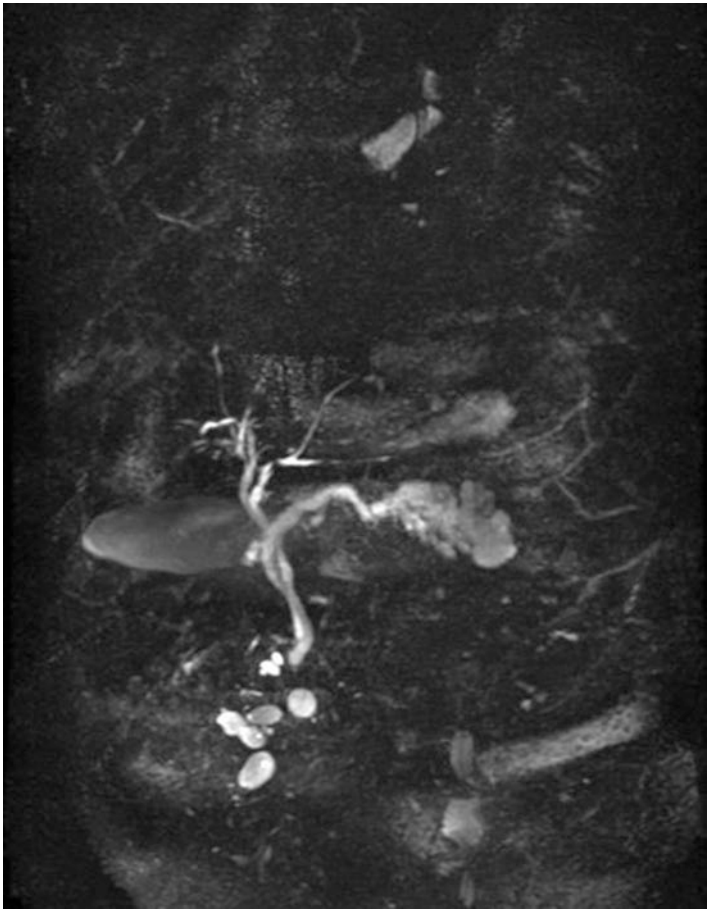

Figure 5.1 MRI image of a main duct IPMN

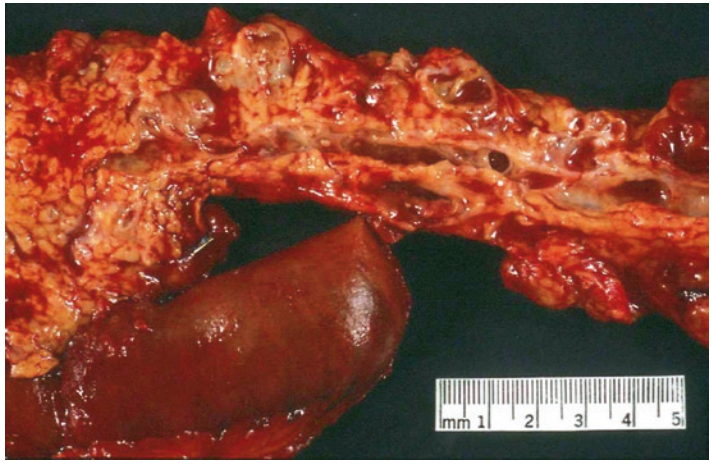

FIGURE 5.2 Resection specimen demonstrating a main duct IPMN

  - BD-IPMN: These are the most common cysts found incidentally on imaging. They can present as solitary cysts or as multiple lesions across the pancreas. BD-IPMNs are often asymptomatic and their potential for malignancy varies based on features such as size, presence of mural nodules, and main pancreatic duct dilation. The rate of malignancy for these cysts is lower than for MD-IPMNs (15–20%), and they do not always warrant a resection [2, 4].

- Serous cystadenoma (SCA): SCAs make up about 16% of all resected pancreatic cysts [2]. They tend to present as isolated lesions. Classic SCAs are composed of multiple cysts with a "honeycomb" appearance and a characteristic central fibrotic scar [2, 4]. These cysts occur in patients over 60 years of age, and they have a male predominance if macrocystic and female predominance if microcystic [4]. SCAs are usually hypervascular [4] and lined by cuboidal epithelium [2]. They can occasionally present with abdominal pain, but most frequently they are asymptomatic. A small fraction of SCAs are secondary to mutation in *VHL* (von Hippel Lindau gene).

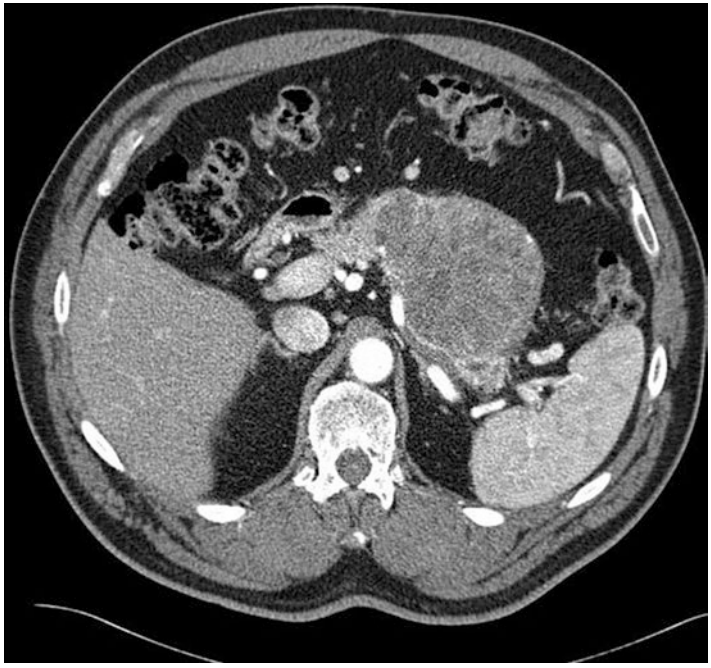

FIGURE 5.3 CT scan image of a large serous cystadenoma in the tail of the pancreas

SCAs generally require resection only if they are causing symptoms due to size rather than concern for malignancy [2]. See Figs. 5.3 and 5.4.

- Solid pseudopapillary neoplasia (SPN): These are rare (3% of all resected pancreatic cysts) tumors found almost exclusively in women in their 20s and 30s who are symptomatic on presentation with abdominal pain or, less frequently, jaundice or pancreatitis. Risk of malignancy is 10–20% and warrants surgical resection [2, 4]. Five-year postoperative survival is 80%, with rare recurrences noted up to a decade after initial presentation [2]. See Figs. 5.5 and 5.6.
- Cystic pancreatic endocrine neoplasm (CPEN): Rarely, pancreatic neuroendocrine tumors may be cystic rather

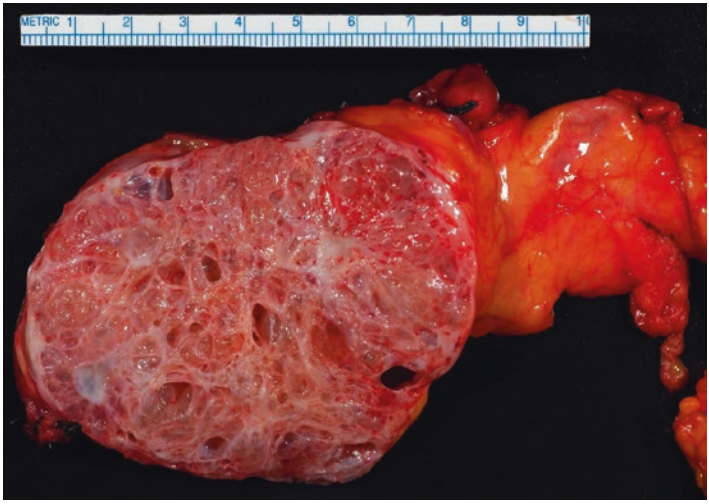

FIGURE 5.4 Resection specimen demonstrating a large serous cystadenoma

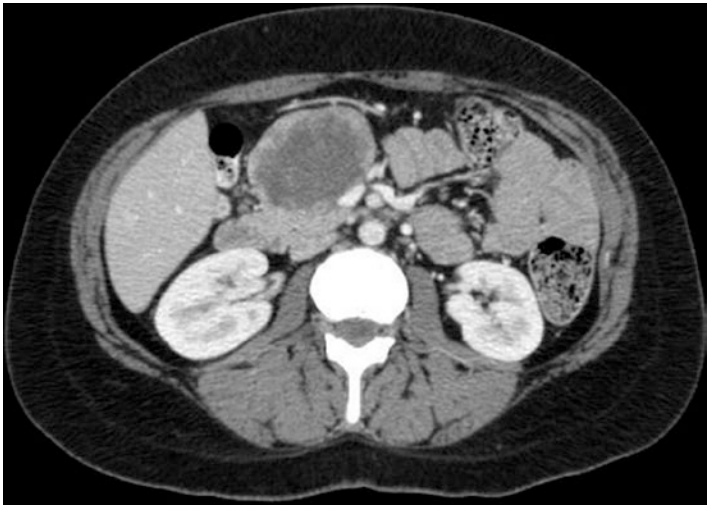

FIGURE 5.5 CT scan demonstrating a solid pseudopapillary tumor of the pancreas

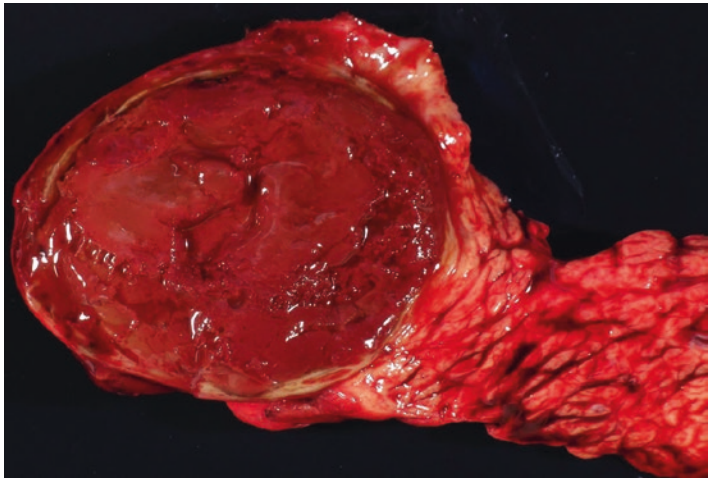

FIGURE 5.6 Resection specimen demonstrating a large pseudopapillary tumor of the pancreas

than solid. These tumors generally occur after age 50 and are found equally in women and in men. They are associated with multiple endocrine neoplasia (MEN-1) syndrome and the *MEN-1* gene mutation. On imaging they reveal enhancement of the cyst wall. Cyst fluid positive for chromogranin A and synaptophysin is both a sensitive and specific finding in these patients. Once disease is confirmed, most patients undergo resection with survival rate of over 87% at 5 years. Risk of malignancy with these tumors is 11–14% [2].

Based on the findings in our patient, her most likely diagnosis is BD-IPMN, although an MCN or a serous cyst (SCA, CPEN) cannot be excluded. Of note, lack of history of pancreatitis makes a pseudocyst unlikely.

Our patient underwent an abdominal MRI as part of her initial workup. Abdominal imaging with an MRI (with or

without contrast) or with a pancreas protocol CT is the first step in both characterizing and risk stratifying the lesion [1–6]. If the diagnosis is still uncertain based on clinical and imaging findings, or if there are additional risk factors, an endoscopic ultrasound with fine needle aspiration (EUS/FNA) may be pursued. Risk factors that prompt further workup include symptomatic initial presentation with obstructive jaundice or pancreatitis, main duct dilation (diameter of 5–9 mm is considered worrisome, while >10 mm is high risk), cyst size >3 cm, and a mural nodule within the cyst [1, 2, 5, 6]. According to the 2012 International Association of Pancreatology guidelines, one risk factor is sufficient to recommend EUS, while the 2015 American Gastroenterological Association guidelines require at least two risk factors [1]. In the case of our patient, her cyst size and possible mural nodule warrant a referral for EUS/FNA.

EUS/FNA can help visualize the cyst better, evaluate possible connections to the pancreatic ducts, visualize a potential mural nodule, and sample the cyst fluid for cytology. EUS/FNA results are still largely operator dependent [1, 5]. Findings on FNA may also vary significantly; thus, the presence of a marker can help classify cysts better, but the absence of one is more difficult to interpret. A useful finding on FNA is the presence of a "string sign" (when cystic fluid stretches between two surfaces over 1 cm), which is highly specific for mucinous cysts [1, 4]. Low amylase levels in the fluid rule out a pseudocyst; however, high levels of amylase are seen in both pseudocysts and in mucinous cysts [1, 4]. CEA levels on cytology are helpful if elevated over 192–200 ng/ml in identifying mucinous cyst (MCN or IPMN), as they are typically low in serous cysts or pseudocysts; CEA is not a predictor of malignancy, however [1, 2, 4–6]. Further, while cytology findings are rare, they can be highly specific, especially if atypical epithelial cells are found [1, 5]. Mutations in *GNAS* or *KRAS* are very specific for IPMNs (>90%, with one of the two mutations present in over 95% of all IPMNs),

but these findings have not been fully validated and are not used on a daily basis [1, 4–7]. Finally, work is underway to identify additional markers within the cyst fluid, such as miRNAs and VEGF [2, 5, 7].

Management

Management of an asymptomatic patient without red flags on imaging is generally limited to serial imaging to monitor progression. The 2012 IAP guidelines recommend surveillance with CT/MRI with frequency that depends on the cyst size [1, 6]. The 2015 AGA recommendations simplify the algorithm and recommend MRI in 1 year, with follow-up studies every 2 years for up to 5 years if no changes are noted [1, 5].

Surgical resection should be discussed if findings suggest high risk of malignancy and the patient is likely to tolerate the procedure. The type of surgery and extent of pancreatic resection depend on the features and location of the cyst within the pancreas. Follow-up imaging after surgery for MCNs and SCAs is only indicated if there is clear pathological evidence of invasion [1, 5, 6]. On the other hand, surveillance recommendations for IPMNs postoperatively vary based on the guidelines. According to the IAP, imaging should be repeated at 2 and 5 years even if no evidence of invasive disease was found, and in the case of dysplasia on pathology—every 6 months; if invasive cancer is found on resection, the patient should be followed based on guidelines for management of pancreatic ductal adenocarcinoma (PDAC). The AGA, on the other hand, recommends postoperative surveillance by MRI every 1–2 years only for significant dysplasia or invasive disease [1, 5].

For the subgroup of patients that meets indications for surgery but cannot undergo surgery for other health reasons, new treatments are being designed, such as injecting cysts with ethanol via EUS or thermally ablating them via EUS or

percutaneously, but these have not been validated and are not commonly used yet [3].

Outcome

The cyst prevalence in the general population has been estimated at 2.5%, and among patients with pancreatic cysts, adenocarcinoma is found in 33.2 per 100,000 with increasing prevalence by age [8]. Thus, the overall risk of malignancy is very low. If a cyst does not meet criteria for resection or does not change in size or other characteristics after 5 years of surveillance, then the patient does not need any additional follow-up and has no greater risk of pancreatic cancer than the general population [5]. Patients who undergo surgery and show no evidence of invasion also have excellent prognosis (80–100% 5-year survival) [2, 5], while those with evidence of invasive cancer have variable survival rates, with an average five year survival for IPMNs around 28% [2, 5].

It is important to keep in mind that only about 15% of patients who undergo surgery have evidence of invasive cancer [1, 4]. Data for IPMNs shows that only 42% of patients who had surgery had either dysplasia or evidence of malignancy [1]. Thus, over half of the patients with pancreatic cysts undergo surgery unnecessarily even after the best available diagnostic technology and predictive analyses are used. Much work is done in identifying better potential cyst fluid markers that can aid diagnosis and predict malignant potential, but they have not been well validated clinically [1, 2, 7]. Further, our ability to rule out malignancy is also disappointing; in a large German medical center, nearly 40% of preoperative diagnoses of MCN or BD-IPMN were found to be wrong [4]. Thus, patients like the one in our case will potentially have to make difficult treatment decisions, and an in-depth discussion with their physician about the risks and benefits of surgical intervention will be key in guiding decision making.

Clinical Pearls/Pitfalls

- Pancreatic cysts are most frequently found incidentally on imaging and have a low overall risk of malignancy.
- The patient profile (age and gender), past medical and family history, as well as clinical presentation can point to the type of cyst the patient has. Young women, for example, are more likely to have SPN or SCAs, while rare patients with family history of MEN may be more likely to have a CPEN. Elderly male smokers, on the other hand, are more likely to present with an IPMN.
- MRI abdomen with contrast or pancreas protocol CT can characterize the cyst and help stratify the risk based on pancreatic duct size, cyst size, or presence of a mural nodule.
- Findings on EUS/FNA can help determine exact cyst type or possibly show evidence of dysplasia or malignancy; however, negative EUS/FNA cytology does not rule out malignancy
- EUS/FNA is not a routine study for all cysts but suggested for patients with worrisome findings on imaging or other risk factors.
- Surveillance by MRI or CT is recommended for patients with serous cysts, as well as for ones with mucinous cysts that do not have worrisome features or evidence of dysplasia or invasion. If no change is noted after 5 years, no additional surveillance is needed.
- Surgery may be recommended for patients with mucinous cysts that have worrisome features and are growing, dysplastic, or otherwise concerning for malignancy, as well as for patients with large symptomatic serous cystadenomas or with SPN. Postsurgical surveillance is needed for patients with positive margins or dysplasia/invasive cancer on pathology.
- At present there is no good blood marker or definitive cyst fluid marker to determine malignant potential for pancreatic cysts.

- Given overall low risk for malignancy, an in-depth discussion of the risks and benefits of surgery and shared decision making can reduce unnecessary procedures and meet individual patient goals.

References

1. Chiang AL, Lee LS. Clinical approach to incidental pancreatic cysts. World J Gastroenterol. 2016;22(3):1236. Available from: http://www.wjgnet.com/1007-9327/full/v22/i3/1236.htm.
2. Kim TS, Fernandez-del Castillo C. Diagnosis and management of pancreatic cystic neoplasms. Hematol Oncol Clin North Am. 2015;29(4):655–74. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0889858815000520.
3. Al-Hawary MM, Francis IR, Anderson MA. Pancreatic solid and cystic neoplasms. Diagnostic evaluation and intervention. Radiol Clin North Am. 2015;53(5):1037–48. Available from: http://dx.doi.org/10.1016/j.rcl.2015.05.005.
4. Jenssen C, Kahl S. Management of incidental pancreatic cystic lesions. Viszeralmedizin. 2015;31(1):14–24.
5. Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):824–48. Available from: http://dx.doi.org/10.1053/j.gastro.2015.01.014.
6. Tanaka M, Fernandez-Del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183–97.
7. Majumder S, Chari ST, Ahlquist DA. Molecular detection of pancreatic neoplasia: Current status and future promise. World J Gastroenterol. 2015;21(40):11387–95.
8. Gardner TB, Glass LM, Smith KD, Ripple GH, Barth RJ, Klibansky DA, et al. Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. Am J Gastroenterol. 2013;108:1546–50. Available from: http://www.nature.com/ajg/journal/v108/n10/pdf/ajg2013103a.pdf.

Chapter 6
Medical and Endoscopic Management of Chronic Pancreatitis

Kartik Sampath and Timothy B. Gardner

Case Study

A 42-year-old male presented to the emergency room (ER) with severe upper abdominal pain radiating to the back. The patient described chronic upper abdominal pain at baseline for the past year; however the pain severity necessitated the ER visit. In the ER, the patient's vitals were stable; however he was in mild distress and received intravenous hydration and hydromorphone.

The past medical history was notable for chronic pancreatitis, which was related to heavy chronic alcohol use over the

K. Sampath, MD (✉)
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Kartik.Sampath@Dartmouth.edu

T.B. Gardner, MD
Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.b.gardner@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_6,

past 22 years. Six years ago, the patient was first diagnosed with acute pancreatitis requiring hospitalization. Alcohol use persisted and the patient eventually developed recurrent acute pancreatitis (RAP) attacks. An abdominal CT scan 1 year ago revealed pancreatic calcifications. At that time, the patient was diagnosed with chronic pancreatitis; tramadol was initiated for chronic pain control. The patient subsequently quit alcohol intake. Despite alcohol cessation, 2 months prior to the ED visit, the patient had another AP episode.

The patient has no prior surgical history. He does endorse an active 12-pack-year smoking history. Family history was notable for alcoholism, without any history of familial pancreatitis or gastrointestinal-based malignancy.

The physical exam was notable for midepigastric tenderness. Labs were normal except for a lipase elevation to 234 units/L (upper limit of normal is 60 units/L). The patient was admitted to the medicine service for aggressive fluid resuscitation. On hospital day 2, a CT abdomen was performed which revealed evidence of a large pancreatic head duct (PD) stone, with proximal PD dilation (Fig. 6.1).

My Management

A. Continue IV hydration and follow-up in GI clinic as an outpatient
B. ERCP with pancreatogram and PD stone removal
C. Aggressive intervention for alcohol and tobacco cessation.

Diagnosis and Assessment

In the setting of chronic alcohol use, this patient has had RAP attacks. A prior CT scan noted pancreatic calcifications, and the patient has had baseline chronic pancreatitis-type pain

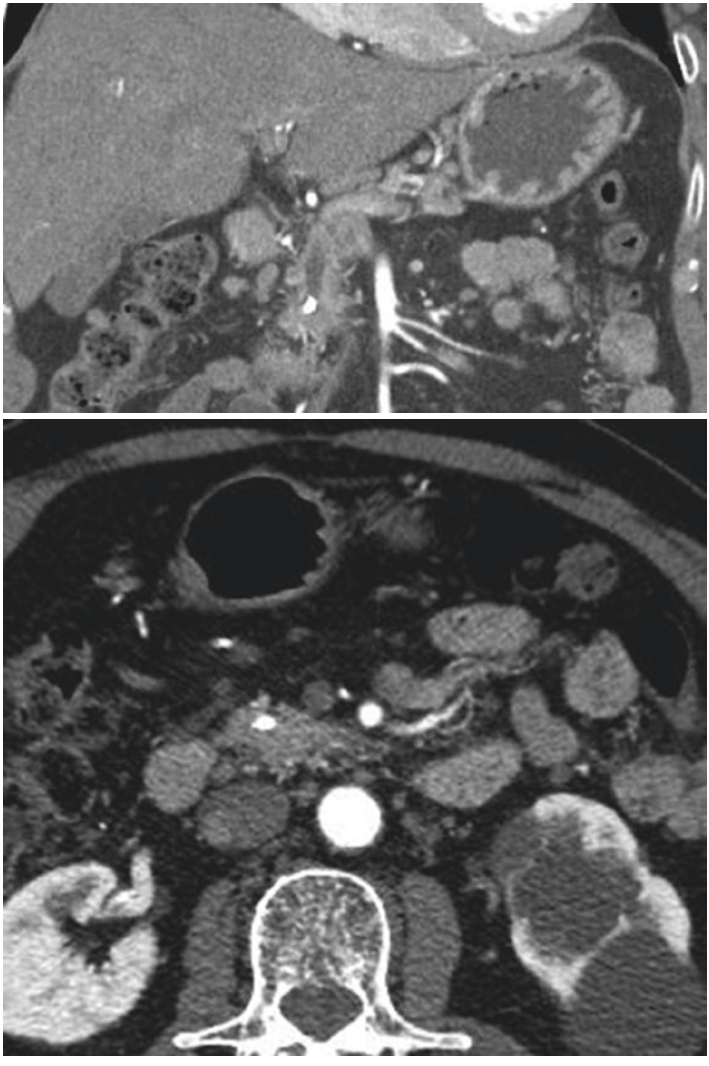

FIGURE 6.1 CT of the pancreas notes a pancreatic ductal head stone with proximal pancreatic duct dilation

for the past year. Based on the clinical presentation, this patient had alcoholic chronic pancreatitis. A key concern in the history is recurrent AP despite alcohol cessation. The CT revealed evidence of a PD stone with ductal obstruction, which likely represents the cause for this patient's current acute on chronic pancreatitis.

CP represents the progression of chronic pancreatic inflammation to irreversible fibrosis, which ultimately can lead to chronic upper abdominal pain and the compromise of pancreatic endocrine and exocrine function [1]. Progressive fibrosis can lead to both pancreatic parenchymal changes and duct abnormalities leading to impaired ductal outflow. CP can be further sub-stratified into large and small pancreatic duct disease with and without calcifications. Standard labs including lipase are often normal in symptomatic CP patients.

Endocrine dysfunction manifests typically as diabetes mellitus (DM). Management includes initiation of oral hypoglycemics and insulin supplementation as needed. New onset diabetes in the setting of chronic pancreatitis is associated with an increased risk for pancreatic cancer [2]. In this scenario, follow-up cross-sectional imaging may be recommended.

Exocrine pancreatic insufficiency (EPI) is due to the impaired synthesis and/or pancreatic secretion of luminal bicarbonate and digestive enzymes (lipase-protease-amylase) [3]. Patients develop steatorrhea as well as vitamin B12 and fat-soluble vitamin (K-A-D-E) deficiencies. The gold standard for EPI is quantitative fecal fat testing where patients are subjected to a high-fat diet (100 g of fat/day), with subsequent stool collection. A fecal fat excretion greater than 7 g/day is diagnostic of EPI. A qualitative stool fat test (Sudan red staining) is no longer recommended due to poor specificity. Elastase is a pancreatic enzyme, excreted via the gut. In EPI, fecal elastase concentrations decline, and a concentration less than 200 mg/g of stool can suggest the EPI diagnosis [4]. In an effort to detect early EPI, pancreatic function tests (PFTs) can be performed. For example, patients can be given IV secretin

followed by direct aspiration of peri-ampullary pancreatic secretions [5]. EPI is diagnosed with duodenal aspirate bicarbonate concentrations less than 80 mEq/L. Endoscopic PFTs demonstrate a sensitivity and specificity of 82% and 86%, respectively, for the EPI diagnosis.

Abdominal imaging is necessary for the CP diagnosis. Abdominal X-ray can reveal pancreatic calcifications which are pathognomonic for CP. In progressed disease, the CT abdomen will note calcifications along with an atrophic pancreas (Fig. 6.2). EUS is an increasingly utilized modality to evaluate chronic pancreatitis and can characterize both parenchymal disease (lobularity, hyperechoic foci and strands, calcifications, cysts) and ductal disease (hyperechoic pancreatic duct walls, irregular pancreatic duct, dilated pancreatic duct, visible side branches) [6]. When five or more criteria are met, CP becomes increasingly more likely. MRCP can also be a valuable imaging modality to characterize ductal-based disease.

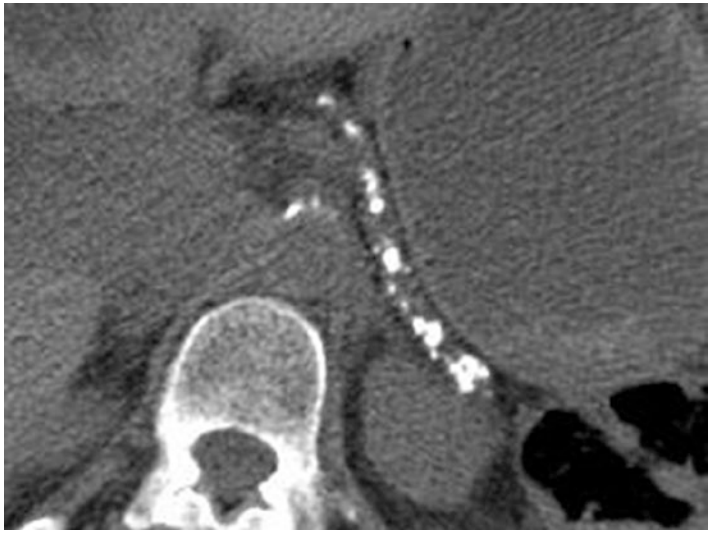

Figure 6.2 CT imaging revealing evidence of chronic pancreatitis with extensive calcifications and a small atrophic appearing pancreas

The classic triad of pancreatic calcifications, steatorrhea, and diabetes mellitus is highly specific but often occurs very late in the progression of chronic pancreatitis. Typically there is evidence of CP on imaging (abdominal X-ray, CT, MRCP, and EUS) along with pancreatitis pain, diabetes, and/or fat malabsorption.

Pancreatitis-type abdominal pain is the most common clinical manifestation of CP. Type A pain refers to frequent severe episodic pain versus type B pain, which can be more prolonged and persistent. Over time, CP pain can become debilitating and lead to a severely impaired quality of life [7].

The exact pathogenesis related to CP pain is not completely understood. It has been proposed that ductal hypertension and microvascular ischemia contribute to the development of CP pain. Ductal hypertension refers to the sequelae of reduced pancreatic duct outflow which leads to pancreatic ductal reflux and chronic pancreatic injury.

Management

In the acute pain exacerbation setting, the first consideration is to identify if there is evidence of acute on chronic pancreatitis. If this is the case, then management involves admission for IV hydration and pain control.

The necessity for CP medical management is predicated on the presence of debilitating symptoms resulting in impaired functionality. Initial management involves the elimination of modifiable risk factors such as smoking and alcohol intake. Dietary modification with small, low-fat meals can contribute to pain relief by moderating pancreatic enzyme secretion and reducing fat malabsorption. For patients with EPI, pancreatic enzyme supplementation allows for fat digestion which can decrease postprandial dyspepsia and steatorrhea.

Analgesic management employs a stepwise approach, beginning with nonnarcotics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Neuropathic agents such as tri-cyclic antidepressants (TCAs—nortriptyline,

amitriptyline), serotonin and norepinephrine reuptake inhibitors (duloxetine), and GABA agonists (pregabalin) can offer pain relief and afford an opportunity to avoid or delay the use of narcotics [8]. If pain symptoms persist, a trial with a low-dose narcotic such as tramadol can be considered, followed in succession by more potent narcotics such as fentanyl or hydromorphone.

Pancreatic enzyme replacement therapy for pain control has been investigated. In theory, exogenous pancreatic enzyme supplementation reduces endogenous pancreatic duct secretions and ductal hypertension. Numerous randomized controlled trials evaluated the efficacy of pancreatic enzyme supplementation for chronic pancreatitis pain relief. A meta-analysis summarizing these trials revealed no significant pain benefit from enzyme supplementation [9].

Medical marijuana has been utilized off-label as a treatment option for CP-related pain and nausea relief. Further study will be needed to definitively characterize the potential therapeutic benefits. Antioxidant therapy and radiotherapy have also been investigated; however larger trials are needed to further validate these therapies.

Pancreatic endotherapy can be utilized for patients who are refractory to medical management. CP-related ductal abnormalities include PD stones, PD strictures, or extrinsic compression from a focal fibrotic mass. In these cases, endoscopic management with ductal decompression can be considered [10]. Pancreatic sphincterotomy is performed to facilitate pancreatic duct drainage. For PD stone management, the limitations of pancreatic endotherapy should be considered. In cases with numerous stones and distally located PD stones, stone removal can be technically difficult. In these cases the risks may outweigh the benefits for pancreatic ERCP.

In our case study patient, a single stone is located in the proximal PD with associated PD dilation. This patient scenario represents the ideal candidate for endotherapy. Options for endoscopic stone removal include forceps removal, basket-based removal, and balloon extraction. A through-the-scope

mechanical lithotripsy is no longer used due to high complication rates. For proximal PD stone disease, stone removal rates can be successful in up to 50% of cases. Extracorporeal shock wave lithotripsy (ESWL) can fracture PD stones and can improve stone clearance rates up to 70% [11]. Direct pancreatoscopy with electrohydraulic lithotripsy (EHL) can be utilized; however the reported experience thus far has been limited.

Pancreatic ductal outflow can also be impaired due to CP-related ductal stricturing disease. Following sphincterotomy, plastic stenting of the stricture can be performed with interval stent replacement. During stent placement, stricture dilation can be considered with a bougie dilator, a Soehendra dilator, or balloon dilation [12]. If a refractory stricture is noted, side by side plastic stents can be employed or a self-expanding metal stent (SEMS) can be placed. In addition to PD strictures, CP can cause biliary-based strictures and gastric outlet obstructions. Biliary obstructions can be treated similarly with periodic plastic stents with focal stricture dilation. SEMS placement is reserved for refractory CP biliary strictures. Duodenal self-expanding metal stents can be placed to alleviate gastric outlet obstructions.

A 2007 NEJM randomized controlled trial (RCT) compared endoscopic versus surgical management for chronic pancreatitis pain management. The results revealed significantly improved pain relief with the surgical treatment arm [13]. While there were flaws related to study design and endoprosthesis use, the study does highlight the potential therapeutic benefits of surgical intervention for significant CP ductal-based disease. We advocate for pancreatic ERCP for CP structuring disease and selected PD stone cases (few stones, located in the proximal PD). In CP cases with complicated ductal pathology, it is important to collaborate with the hepatobiliary surgeons to determine the optimal management strategy.

EUS neurolysis represents a therapeutic option for symptomatic parenchymal disease. Current EUS-based neurolysis therapies include direct injection of bupivacaine or

triamcinolone into the celiac plexus [14]. Unfortunately, EUS neurolysis has demonstrated poor pain relief efficacy in the long term, with only 10% of patients experiencing prolonged benefits at 24 weeks post neurolysis [15]. From a chronic pancreatitis standpoint, EUS neurolysis should be considered in poor surgical candidates or as a potential bridge to eventual surgical intervention.

Surgical options for chronic pancreatitis include the Puestow procedure, Frey procedure, Whipple procedure, and Total Pancreatectomy Islet Auto-Transplantation (TPIAT). Further discussion of surgical-based intervention for chronic pancreatitis will be discussed in a separate chapter.

Outcome

In this case, one localized stone is noted in the proximal pancreatic duct with corresponding PD dilation. An ERCP with pancreatic duct sphincterotomy was performed. The guidewire was unable to be advanced past the stone. A pancreatic duct stent was placed, followed by EWSL of the stone. In a follow-up, serial imaging revealed successful stone clearance. The patient continued to do well clinically with no subsequent AP attacks and no further escalation of his baseline analgesic medication requirements.

Clinical Pearls/Pitfalls

- CP represents a fibroinflammatory condition that may or may not be preceded by recurrent acute pancreatitis.
- CP can be difficult to diagnose during the early stages of the disease.
- CP is diagnosed by a combination of abnormal pancreatic imaging (CT/MRI/EUS) with evidence of chronic abdominal pain or pancreatic insufficiency (diabetes/fat malabsorption).

- Endocrine dysfunction is screened with a hemoglobin A1c and managed with oral hypoglycemics and insulin supplementation.
- Exocrine dysfunction is screened with quantitative fecal fat testing and stool elastase. Treatment includes exogenous oral pancreatic enzyme (lipase/protease/amylase) supplementation.
- Chronic pancreatitis pain is managed in a stepwise manner initially with nonnarcotics, neuropathic agents, and eventually narcotics.
- Pancreatic enzyme supplementation does not have definitive clinical benefit for chronic pancreatitis pain relief.
- Pancreatic endotherapy is a therapeutic option that must be considered on a case-by-case basis.
- Pancreatic ERCP for PD stone removal is more successful for a few proximal located stones.
- Pancreatic ERCP-based stenting can be considered for dominant focal strictures.
- EUS celiac block can treat parenchymal-based pain; however long-term benefits are minimal. EUS neurolysis should be utilized as a bridge to surgery or for nonsurgical candidates.

References

1. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. Pancreatology. 2016;16(2):218–24.
2. Illés D, Terzin V, Holzinger G, et al. New-onset type 2 diabetes mellitus—a high-risk group suitable for the screening of pancreatic cancer? Pancreatology. 2016;16(2):266–71.
3. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. Gut. 2005;54(Suppl 6):vi1–28. Review.
4. Keim V, Teich N, Moessner J. Clinical value of a new fecal elastase test for detection of chronic pancreatitis. Clin Lab. 2003;49(5–6):209–15.

5. Ketwaroo G, Brown A, Young B, et al. Defining the accuracy of secretin pancreatic function testing in patients with suspected early chronic pancreatitis. Am J Gastroenterol. 2013;108(8):1360–6.
6. Gardner TB, Taylor DJ, Gordon SR. Reported findings on endoscopic ultrasound examinations for chronic pancreatitis: toward establishing an endoscopic ultrasound quality benchmark. Pancreas. 2014;43(1):37–40.
7. Drewes AM, Krarup AL, Detlefsen S, et al. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. Gut. 2008;57(11):1616–27.
8. Olesen SS, Juel J, Graversen C, et al. Pharmacological pain management in chronic pancreatitis. World J Gastroenterol. 2013;19(42):7292–301.
9. Brown A, Hughes M, Tenner S, et al. Does pancreatic enzyme supplementation reduce pain in patients with chronic pancreatitis: a meta-analysis. Am J Gastroenterol. 1997;92(11):2032–5.
10. Talukdar R, Reddy DN. Pancreatic endotherapy for chronic pancreatitis. Gastrointest Endosc Clin N Am. 2015;25(4):765–77.
11. Talukdar R, Nageshwar RD. Endoscopic therapy for chronic pancreatitis. Curr Opin Gastroenterol. 2014;30(5):484–9.
12. Weber A, Schneider J, Neu B, et al. Endoscopic stent therapy for patients with chronic pancreatitis: results from a prospective follow-up study. Pancreas. 2007;34(3):287–94.
13. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007;356(7):676–84.
14. Gress F, Schmitt C, Sherman S, et al. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. Am J Gastroenterol. 1999;94(4):900–5.
15. Gress F, Schmitt C, Sherman S, et al. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. Am J Gastroenterol. 2001;96(2):409–16.

Chapter 7
Complications of Acute Pancreatitis

Jeffrey M. Adler

Case Study

A 47-year-old man was admitted to a medical intensive care unit for severe acute alcoholic pancreatitis resulting in extensive pancreatic necrosis, as well as respiratory and renal failure. This was his third and most severe admission for alcoholic pancreatitis over the preceding 2 years. He gradually recovered and was discharged home. He returned 3 weeks later with severe abdominal pain. A CT scan of the abdomen revealed extensive pancreatic necrosis, with a large amount of peripancreatic edema and several poorly organized fluid collections, the largest measuring 5.7 cm × 2 cm × 2.7 cm (Fig. 7.1). An MRCP/MRI additionally showed multifocal thrombosed segments of the splenic vein and a disrupted pancreatic duct at the level of the pancreatic mid neck (Fig. 7.2).

J.M. Adler, MD
Section of Gastroenterology, Lebanon, NH 03756, USA
e-mail: Jeffrey.M.Adler@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_7,

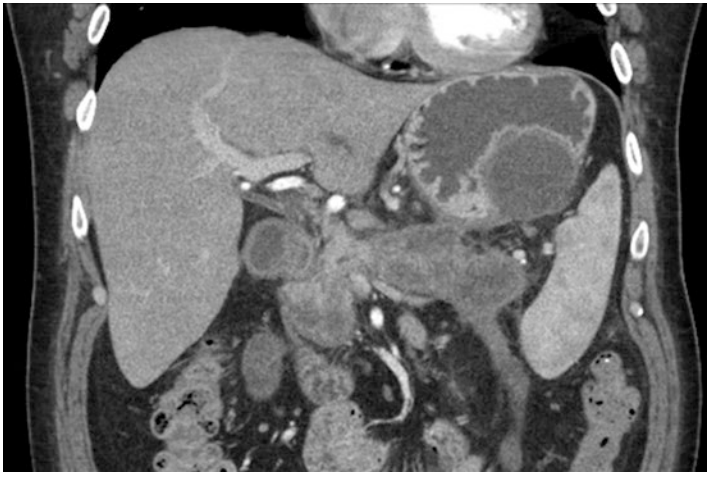

FIGURE 7.1 CT scan of the abdomen with extensive pancreatic necrosis, with a large amount of peripancreatic edema and several poorly organized fluid collections, the largest measuring 5.7 cm × 2 cm × 2.7 cm

My Management

A. Correctly identify the type of fluid collection.
B. Initiate a multidisciplinary evaluation that includes gastroenterology, interventional radiology, and surgery.
C. Anticipate medical management followed by reevaluation for interval endoscopic transmural drainage/debridement.

Diagnosis and Assessment

Acute pancreatitis (AP) begins with an intense inflammatory process within the pancreas that may extend into surrounding tissues. This inflammatory process may also lead to a number of local complications within or around the

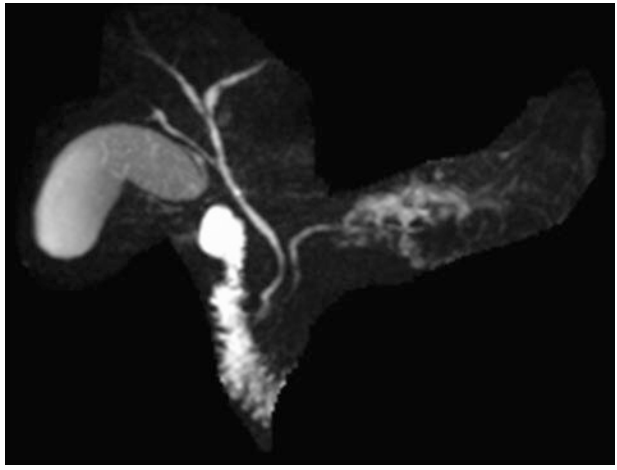

FIGURE 7.2 MRCP showing a disrupted pancreatic duct at the level of the pancreatic mid neck

pancreatic tissue, including the formation of fluid collections, major vascular or bleeding complications, and pancreatic duct disruption.

As per the Atlanta Classification System revised in 2013, fluid collections have been organized into four general categories: (1) acute peripancreatic fluid collections (APFC), (2) pancreatic pseudocysts (PP), (3) acute necrotic collections (ANC), and (4) walled-off necrosis (WON) [1]. These complications represent a progression of local injury that begins early during a patient's episode of AP. There may be early indicators on imaging that local complications will develop; however, these findings and the subsequent development of local complications alone do not imply the patient will experience a severe clinical course [2]. Acute peripancreatic fluid collections, when present, appear early during acute pancreatitis (i.e., within 4 weeks by definition) and generally resolve without major sequelae [3]. These are

non-necrotic collections without a discrete wall, are generally confined by fascial planes, and usually remain sterile. Acute necrotic collections may also develop within the first 4 weeks and are due to necrosis of the pancreas and/or peripancreatic tissues. In very early phases, it may be difficult to differentiate ANC from APFC; however, ANC are usually fairly distinct outward of 1 week from acute pancreatitis and appear as heterogeneous collections with various amounts of semisolid and necrotic debris. Walled-off pancreatic fluid collections are delayed sequelae that usually take over a month to develop and as a group include pancreatic pseudocysts (PP) and walled-off necrosis (WON). Pancreatic pseudocysts represent collections of simple fluid and in general are thought to form in communication with the pancreatic duct system. On the other hand, WON represents an encapsulation of necrotic material within an inflammatory wall that can take weeks to fully mature. On contrast enhanced CT, the wall is often enhancing, but the contents may not always be easily characterized as solid or simple fluid, which may explain why some of these are mislabeled as pseudocysts.

Both ANC and WON may be sterile or become infected, and this may become apparent clinically or on imaging showing gas formation within the collection. In general the diagnosis of infected necrosis can usually be made clinically, although sometimes it can be challenging to differentiate infection from the systemic inflammatory response of necrotizing pancreatitis alone. Sampling the fluid either percutaneously or endoscopically is one way to help establish the diagnosis of infection when in question, but is typically not necessary or desired, having both a low negative predictive value and associated risk of contamination or inoculation [4].

Major vascular complications and hemorrhage develop in a minority of patients with acute pancreatitis. The inflammatory process and proteolytic activity of pancreatic enzymes can injure both local arterial and venous vasculature [5]. Early in a course of acute pancreatitis, these effects have the potential to disrupt the integrity of vessels and cause diffuse

pancreatic hemorrhage or bleeding from a major artery in proximity to the pancreas. These events are rare, occurring in around 0.5% of acute pancreatitis cases [6]. Delayed bleeding, occurring 2 months beyond one or more episodes of acute pancreatitis, is also uncommon and may occur in 1% of cases [7]. The more common sources of these delayed bleeding events are bleeding pseudoaneurysms, diffuse bleeding from pancreatic necrosis, and hemorrhagic pseudocysts. Many of these events can be managed through vascular embolization, but others may require operative care. Peripancreatic venous thromboses also develop in some patients with acute pancreatitis and may result from venous stasis related to mass effect from edema or direct damage to the vessels from the inflammatory milieu [8]. It is not clear from available evidence whether patients should be routinely anticoagulated for this condition.

Acute pancreatitis may also result in pancreatic duct disruption (PDD) and leakage of pancreatic secretions. Some of these leaks resolve spontaneously or with conservative medical management, but they may also persist and lead to pancreatic pseudocysts, internal pancreatic fistulae (IPF) with pancreatic ascites or effusions, or external pancreaticocutaneous fistulae (EPF). In patients with acute necrotizing pancreatitis, the disruption is often complete, meaning that the pancreatic duct proximal to the leak does not opacify on endoscopic retrograde pancreatography (ERP), and is referred to as a disconnected pancreatic duct syndrome (DPDS). The disruption may also only be partial, and evaluation should include assessment for pancreatic duct stricture and calculi, which may impact the approach to therapy. Most of this can now be accomplished noninvasively using contrast enhanced CT or MRCP with or without secretin stimulation, and unlike ERP, these imaging techniques can characterize the anatomy proximal to a complete disruption.

The management and outcome of PDD depends largely on the pancreatic duct anatomy and type of complication that develops as a consequence of duct leakage [9]. Conservative medical management alone is an option in many cases [10],

and small asymptomatic pseudocysts often do not require intervention [11]. When intervention is required, the approach may involve a combination of endoscopic, radiologic, or surgical procedures.

There are few comparative effectiveness trials that have established the preferred management strategy for pancreatic pseudocysts, and selection of technique is usually handled on a case by case basis. However, endoscopic treatment appears to be more effective than percutaneous drainage and is at least as effective and associated with less morbidity and lower costs than surgery [12, 13]. Endoscopic therapy often involves transmural drainage of the fluid collection with stenting across an endoscopic cystogastrostomy or cystenterostomy. While not always practiced, use of endoscopic ultrasonography (EUS) for these procedures has certain advantages and can be generally suggested. Importantly, transmural drainage does not necessarily imply that the disruption will heal, and there is still a risk that the fluid collection will recur once the transmural stents are removed [14]. This is a particular problem in patients with DPDS who may require long-term or permanent transmural stents.

Endoscopic treatment may also involve transpapillary access of the pancreatic ducts and fluid collections. This technique can allow for direct drainage of the collection or be used to place a pancreatic duct stent to redirect the flow of secretions. There is some uncertainty about the efficacy of this approach and concerns about poorer outcomes when used in combination with transmural drainage [15, 16], but it remains an option when a transmural approach is not technically feasible. The benefit may be limited to some cases of partial disruption, and in general the aim should be to bridge the defect with the stent [17, 18]. It is also not clear how long the stent should be left in place, and there is potential for these stents to cause duct injury [19].

In a minority of cases, pancreatic duct disruption can lead to internal fistula and the development of pancreatic ascites and pleural effusions. Medical management in these cases may not be adequate and surgery is associated with significant

morbidity and mortality [20]. Alternatively, endoscopic therapy with pancreatic sphincterotomy and stenting may be an effective option that can provide durable results [21]. External pancreatico-cutaneous fistulae are also encountered infrequently and have traditionally been managed medically, with surgery reserved for refractory cases or those unlikely to resolve spontaneously. Similar to IPF, endoscopic therapy with transpapillary stenting has been used for some of these cases and may also be successful [22].

Management

The patient presented above returned several weeks after an episode of acute necrotizing pancreatitis with severe pain and organizing fluid collections. His symptoms were controlled medically, and follow-up imaging in 1 month showed stability in the size and extent of the collections. He underwent an elective ERP demonstrating complete pancreatic ductal disruption at the mid neck without identification of a proximal remnant, and a pancreatic duct stent was placed into the duct to the site of disruption. He returned a couple of weeks later with fever and chills, and a CT showed enlarging walled-off pancreatic fluid collections with air-fluid levels (Fig. 7.3). Endoscopic cystogastrostomy and placement of a 15 mm lumen apposing covered self-expanding metal stent (LACSEM) was then performed, and copious pus and debris was seen draining across the stent into the stomach.

One important point about this patient's management was that drainage and debridement was not immediately pursued when he returned within a short interval from the episode of acute necrotizing pancreatitis. There are certain limitations and a hazard of pursuing intervention too early in these patients [23], but exceptions are also worth noting. For example, patients with suspected infected necrosis with ongoing sepsis and clinical deterioration often require earlier intervention and should probably be cared for by physicians with specialized expertise in the field. Otherwise, for many cases,

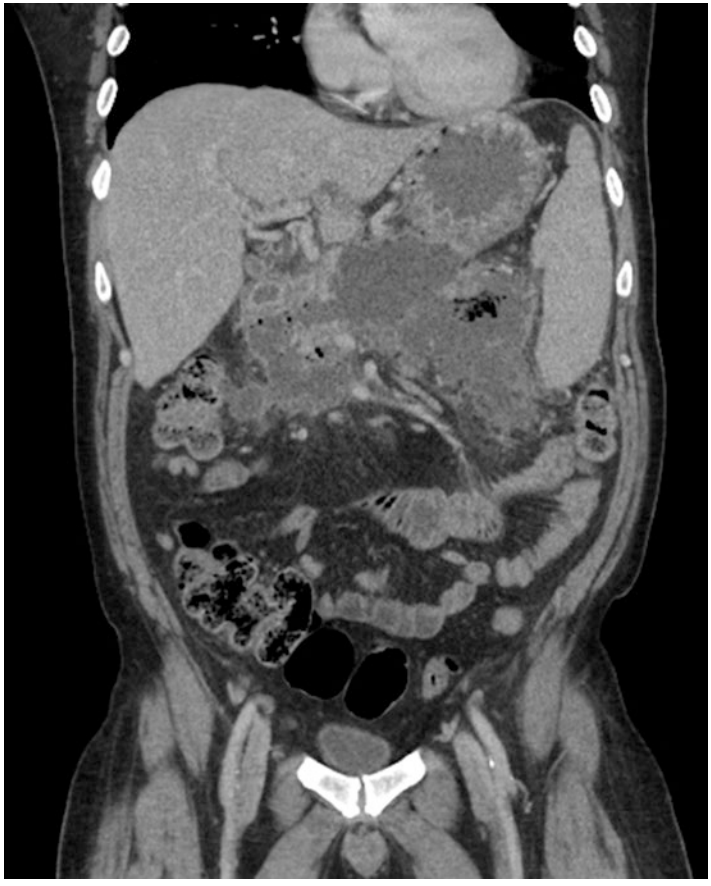

FIGURE 7.3 CT image demonstrating walled-off pancreatic necrosis

there are certain advantages to delaying intervention. The current trend in management is toward endoscopic transmural treatment when feasible [24, 25], but this requires a mature capsule around the collection that usually takes 4–8 weeks to develop. It is for this reason that most endoscopic interventions, if indicated, can be anticipated at least 8 weeks after the initial episode of acute necrotizing

pancreatitis. Other patients with sterile walled-off necrosis may develop a gastric-outlet or biliary obstruction requiring earlier treatment, but the choice to pursue endoscopic intervention in these patients again depends on whether the collection has matured.

The patient above was also found to have a pancreatic duct disruption at the level of the pancreatic head. The decision to pursue transpapillary pancreatic duct stenting in this patient is controversial. Small collections without internal debris that communicate with pancreatic ducts can sometimes be managed effectively with transpapillary stenting; but, in cases where transmural drainage is selected, there may be no additional benefit to adding transpapillary drainage [16]. The argument for transpapillary stenting in duct disruption for patients with walled-off necrosis (as in the above case) is less clear. There have been conflicting results in retrospective analyses that have examined PD stenting as a covariate for treatment success among cohorts that included walled-off necrosis [26, 27]. There has also been some positive experience with direct transpapillary draining of walled-off necrosis in cases where transmural accesses were not technically feasible [28]. The main point to consider is that transmural drainage by itself for WON is highly effective, and there is insufficient evidence to support the need for routine transpapillary stenting in these cases.

Outcome

One month after placing the LACSEM stent, repeat imaging showed near complete collapse of the pancreatic fluid collections and stable position of the pancreatic duct and LACSEM stents. Repeat endoscopy was performed and was successful at retrieving both stents. The patient subsequently did very well clinically, imaging showed near complete resolution of all fluid collections, and he remained abstinent from alcohol and was able to return to work, but in the future required insulin for endocrine insufficiency.

Clinical Pearls/Pitfalls

- Acute necrotizing pancreatitis can lead to a multitude of local complications. The most common are inflammatory fluid collections, vascular and hemorrhagic complications, and pancreatic duct disruptions.
- Endoscopic therapy has emerged as the preferred management strategy for the majority of fluid collections. In general, the timing of endoscopic intervention is influenced by how long it takes for the collection to mature and become fully encapsulated.
- Major vascular complications and bleeding are uncommon, but are associated with a high mortality. These conditions are often handled by vascular embolization, but surgery may at times become necessary. Peripancreatic venous thrombosis is also often identified on imaging, but it is not clear whether these patients should be routinely anticoagulated.
- Pancreatic duct disruptions may contribute to fluid collections or fistulae, but the optimal management strategy depends largely on the individual clinical scenario.

References

1. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11.
2. Vege SS, Gardner TB, Chari ST, Munukuti P, Pearson RK, Clain JE, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include "moderately severe acute pancreatitis". Am J Gastroenterol. 2009;104(3):710–5.
3. Lenhart DK, Balthazar EJ. MDCT of acute mild (nonnecrotizing) pancreatitis: abdominal complications and fate of fluid collections. AJR Am J Roentgenol. 2008;190(3):643–9.

4. ASGE Standards of Practice Committee, Muthusamy VR, Chandrasekhara V, Acosta RD, Bruining DH, Chathadi KV, et al. The role of endoscopy in the diagnosis and treatment of inflammatory pancreatic fluid collections. Gastrointest Endosc. 2016;83(3):481–8.
5. Flati G, Andren-Sandberg A, La Pinta M, Porowska B, Carboni M. Potentially fatal bleeding in acute pancreatitis: pathophysiology, prevention, and treatment. Pancreas. 2003;26(1):8–14.
6. Andersson E, Ansari D, Andersson R. Major haemorrhagic complications of acute pancreatitis. Br J Surg. 2010;97(9):1379–84.
7. Balthazar EJ, Fisher LA. Hemorrhagic complications of pancreatitis: radiologic evaluation with emphasis on CT imaging. Pancreatology. 2001;1(4):306–13.
8. Mortele KJ, Mergo PJ, Taylor HM, Wiesner W, Cantisani V, Ernst MD, et al. Peripancreatic vascular abnormalities complicating acute pancreatitis: contrast-enhanced helical CT findings. Eur J Radiol. 2004;52(1):67–72.
9. Varadarajulu S, Rana SS, Bhasin DK. Endoscopic therapy for pancreatic duct leaks and disruptions. Gastrointest Endosc Clin N Am. 2013;23(4):863–92.
10. Alexakis N, Sutton R, Neoptolemos JP. Surgical treatment of pancreatic fistula. Dig Surg. 2004;21(4):262–74.
11. Cheruvu CV, Clarke MG, Prentice M, Eyre-Brook IA. Conservative treatment as an option in the management of pancreatic pseudocyst. Ann R Coll Surg Engl. 2003;85(5):313–6.
12. Gurusamy KS, Pallari E, Hawkins N, Pereira SP, Davidson BR. Management strategies for pancreatic pseudocysts. Cochrane Database Syst Rev. 2016;4:CD011392.
13. Keane MG, Sze SF, Cieplik N, Murray S, Johnson GJ, Webster GJ, et al. Endoscopic versus percutaneous drainage of symptomatic pancreatic fluid collections: a 14-year experience from a tertiary hepatobiliary centre. Surg Endosc. 2016;30(9):3730–40.
14. Arvanitakis M, Delhaye M, Bali MA, Matos C, De Maertelaer V, Le Moine O, et al. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. Gastrointest Endosc. 2007;65(4):609–19.
15. Shrode CW, Macdonough P, Gaidhane M, Northup PG, Sauer B, Ku J, et al. Multimodality endoscopic treatment of pancreatic duct disruption with stenting and pseudocyst drainage: how efficacious is it? Dig Liver Dis. 2013;45(2):129–33.
16. Yang D, Amin S, Gonzalez S, Mullady D, Hasak S, Gaddam S, et al. Transpapillary drainage has no added benefit on treatment

outcomes in patients undergoing EUS-guided transmural drainage of pancreatic pseudocysts: a large multicenter study. Gastrointest Endosc. 2016;83(4):720–9.
17. Varadarajulu S, Noone TC, Tutuian R, Hawes RH, Cotton PB. Predictors of outcome in pancreatic duct disruption managed by endoscopic transpapillary stent placement. Gastrointest Endosc. 2005;61(4):568–75.
18. Telford JJ, Farrell JJ, Saltzman JR, Shields SJ, Banks PA, Lichtenstein DR, et al. Pancreatic stent placement for duct disruption. Gastrointest Endosc. 2002;56(1):18–24.
19. Sherman S, Hawes RH, Savides TJ, Gress FG, Ikenberry SO, Smith MT, et al. Stent-induced pancreatic ductal and parenchymal changes: correlation of endoscopic ultrasound with ERCP. Gastrointest Endosc. 1996;44(3):276–82.
20. Gomez-Cerezo J, Barbado Cano A, Suarez I, Soto A, Rios JJ, Vazquez JJ. Pancreatic ascites: study of therapeutic options by analysis of case reports and case series between the years 1975 and 2000. Am J Gastroenterol. 2003;98(3):568–77.
21. Pai CG, Suvarna D, Bhat G. Endoscopic treatment as first-line therapy for pancreatic ascites and pleural effusion. J Gastroenterol Hepatol. 2009;24(7):1198–202.
22. Bakker OJ, van Baal MC, van Santvoort HC, Besselink MG, Poley JW, Heisterkamp J, et al. Endoscopic transpapillary stenting or conservative treatment for pancreatic fistulas in necrotizing pancreatitis: multicenter series and literature review. Ann Surg. 2011;253(5):961–7.
23. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011;141(4):1254–63.
24. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362(16):1491–502.
25. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307(10):1053–61.
26. Varadarajulu S, Bang JY, Phadnis MA, Christein JD, Wilcox CM. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of treatment success in 211 consecutive patients. J Gastrointest Surg. 2011;15(11):2080–8.

27. Trevino JM, Tamhane A, Varadarajulu S. Successful stenting in ductal disruption favorably impacts treatment outcomes in patients undergoing transmural drainage of peripancreatic fluid collections. J Gastroenterol Hepatol. 2010;25(3):526–31.
28. Smoczynski M, Jagielski M, Jablonska A, Adrych K. Transpapillary drainage of walled-off pancreatic necrosis - a single center experience. Wideochir Inne Tech Maloinwazyjne. 2016;10(4):527–33.

Chapter 8
Endoscopic Therapy for Complications of Acute Pancreatitis

Jason D. Ferreira

Case Study

A 58-year-old male with past medical history of coronary artery disease requiring previous coronary stent placement, obstructive sleep apnea, and hypertension on aspirin, losartan, and hydrochlorothiazide at home presented after a syncopal event in the setting of significant abdominal pain and diarrhea with further work-up consistent with an initial bout of acute pancreatitis as indicated by elevated lipase and imaging confirmation of peripancreatic inflammation. A work-up of the etiology of his pancreatitis revealed no significant alcohol use, no evidence of cholelithiasis or choledocholithiasis, and normal calcium and triglyceride levels. His symptoms improved after 10 days of conservative management with intravenous fluids and symptom control. He was able to advance his diet, but sub-

J.D. Ferreira, MD
University Gastroenterology, 148 West River Street, Suite 3, Providence, RI 02904, USA
e-mail: Jason.Ferreira1@gmail.com

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_8,

sequently was readmitted to the hospital 3 weeks after discharge with progressive inability to eat due to abdominal pain. Imaging was performed and demonstrated a 9.6 cm by 4 cm pancreatic fluid collection associated with pancreatic necrosis involving the body and tail of the pancreas as shown in Fig. 8.1.

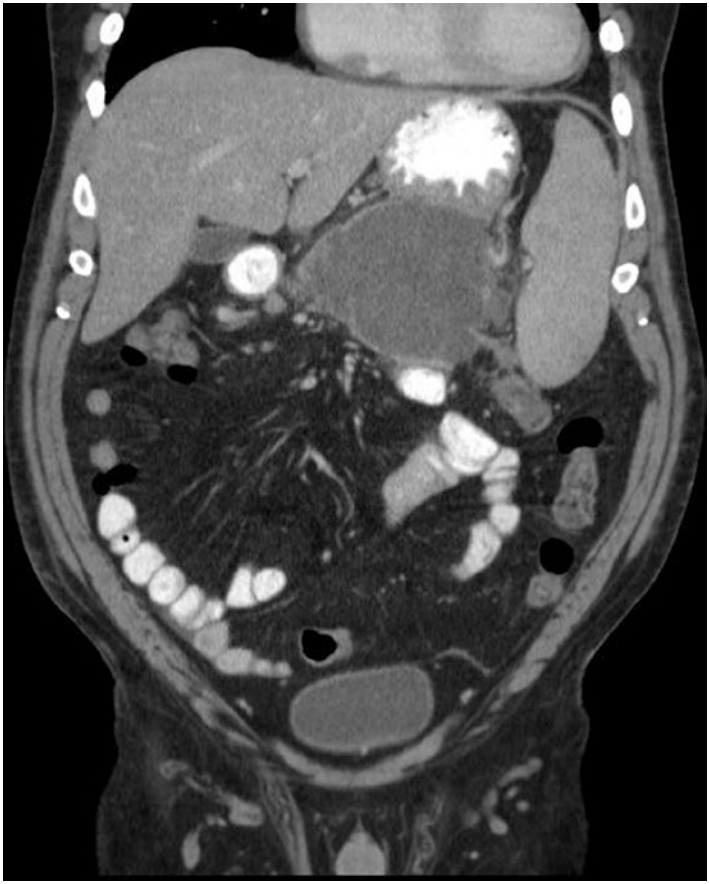

Figure 8.1 A representative coronal CT image of the 9.6 cm by 4 cm peripancreatic fluid collection abutting the stomach

My Management

A. Endoscopic ultrasound to be sure that this does not represent a mucinous neoplasm
B. Endoscopic cystogastrostomy and endoscopic debridement.

Diagnosis and Assessment

When encountering a patient presenting with a bout of acute pancreatitis, clinicians should not only provide aggressive intravenous fluid resuscitation and symptom control but also perform a thorough work-up to determine the etiology of the pancreatitis, use one of several scoring systems to try to predict the severity of disease, and counsel patients on warning signs of possible future complications of pancreatitis. The rationale for aggressive intravenous fluids and the use of scoring systems have been reviewed in other chapters, so my focus here will be to briefly review his work-up in regard to the etiology of his pancreatitis and concentrate mostly on the treatment of walled-off pancreatic necrosis which later developed as a complication of his initial presentation.

Determining the etiology of pancreatitis can be essential to treat the acute episode and prevent future bouts. In this case, it was determined that alcohol did not play a significant role in his illness as he reported drinking alcohol rarely which was corroborated by his wife. He also had a history of tobacco use but had quit smoking after developing coronary artery disease several years earlier. Ultrasound and CT imaging of his gallbladder and biliary system did not reveal any cholelithiasis or choledocholithiasis, and labs revealed normal calcium and triglyceride levels. Although he did present with an unwitnessed syncopal event, it was not felt that he sustained any trauma to his abdomen as a result of his fall, and it was likely the severe pain of his pancreatitis and dehydration

from diarrhea that precipitated syncope. Drug-induced pancreatitis was entertained secondary to his losartan or hydrochlorothiazide use, but he had been stable on that drug regimen for several years.

His first admission was complicated by severe acute kidney injury requiring brief renal replacement therapy before complete renal function recovery likely due to the severity of his dehydration secondary to diarrhea on presentation. The conclusion of his first admission was that the etiology of his pancreatitis was indeterminate and thought possibly to be drug induced, microlithiasis related, or possibly idiopathic. His previous home antihypertensive regimen was discontinued, and although he improved greatly, he continued to have progressive pain after eating and diarrhea after hospital discharge.

It was not until his second admission, 4.5 weeks after his initial presentation for worsening abdominal pain, when the true etiology of his pancreatitis was determined after an infectious work-up took place due to persistent fevers, elevated white count, and ongoing diarrhea that revealed positive stool and blood cultures for *Salmonella*. Infection is an uncommon cause of pancreatitis in adults, and it is not recommended to routinely screen for infection as an etiology for pancreatitis in the absence of infectious symptoms. Of interest, his wife had also mild diarrheal illness related to *Salmonella* diagnosed around the time of his initial presentation.

Unfortunately, likely due to his severe dehydration on initial presentation and subsequent severe pancreatitis with renal dysfunction requiring renal replacement therapy, he developed pancreatic necrosis, which over the course of weeks from his initial presentation had evolved into walled-off pancreatic necrosis or WOPN. Given his elevated white count and persistent fevers, he underwent percutaneous aspiration of the WOPN with subsequent fluid culture revealing *Salmonella*. He continued to have significant pain, which limited his oral intake thought to be secondary to the WOPN requiring the initiation of total parenteral nutrition to ensure he was meeting his caloric needs.

Management

When encountered with symptomatic WOPN, there are several different approaches that can be considered for treatment. Those patients with no or minimal symptoms could be managed expectantly with watchful waiting and serial imaging. Studies of this approach performed in the 1990s suggest that about 60% of patients followed in this manner have complete resolution of the pancreatic collection over time, whereas the remaining patients developed a complication or required surgical management [1, 2].

The traditional treatment for WOPN would be open or laparoscopic surgical necrosectomy. This technique may still be practiced routinely in areas where radiologic guided or endoscopic drainage procedures are not available, but in general is not favored due to its invasiveness and evidence of worse patient outcomes that have been documented in several studies. Open surgical drainage can be accomplished by surgical resection of the area in question or surgically created cystenterostomies or cystogastrostomies for drainage. Laparoscopic surgical necrosectomy would possibly involve a distal pancreatectomy if the collection was in the body or tail or the creation of a cystogastrostomy, cystenterostomy, or drainage via the creation of a Roux limb of the jejunum. Contemporary studies comparing surgical necrosectomies and less invasive approaches continue to suggest higher morbidity and mortality with surgical techniques with one retrospective study showing higher rates of sepsis and persistent multiorgan dysfunction (73.3 vs. 44.7%), higher mortality (33.3 vs. 10.5%), and higher rates of diabetes (33.3 vs. 4.7%) when comparing surgical to less invasive techniques [3]. Surgical approaches may still be required if the collection is not amenable or is refractory to an endoscopic or radiologic approach.

Percutaneous catheter drainage remains another option for the treatment of WOPN that can be as effective as a surgical approach. This technique uses radiology guidance to establish percutaneous access into the pancreatic

collection to allow the placement of a drainage catheter which can then be upsized over time to allow for the removal of necrotic debris. Advantages of this technique include its minimally invasive nature and lower associated mortality rate, but disadvantages include the possibility of creating a pancreaticocutaneous fistula and infection of the drain track. Studies of percutaneous drainage for WOPN have demonstrated it to be a feasible stand-alone treatment in a little less than 50% of patients [4, 5] with one study of 34 patients showing a 12% mortality rate in four out of eight patients that failed to show clinical improvement after a percutaneous approach who eventually required surgical drainage [4]. In one series of 52 patients, it took a mean of 42 days to drain the WOPN by a percutaneous approach [6]. The current role of percutaneous drainage is in the management of retroperitoneal WOPN that may not be amenable to endoscopic therapy or to stabilize septic patients prior to a surgical or endoscopic approach.

Endoscopic management of WOPN is the gold standard approach in areas where expertise in this technique is available and in cases where the WOPN is abutting the lumen of the gastrointestinal tract. Multiple studies have established endoscopic therapy to have the highest degree of success with the least amount of morbidity and mortality when treating WOPN. The minority of patients with relatively small pancreatic collections in communication with the main pancreatic duct or pancreatic ductal disruption are good candidates for transpapillary stent placement through an ERCP alone as therapy, but the vast majority of patients with larger collections will require endoscopic necrosectomy.

Endoscopic necrosectomy involves transmural puncture through the wall of the stomach or duodenum directly into the WOPN. This is primarily done under endoscopic ultrasound guidance but at times can be performed under endoscopic guidance alone in instances where the bulge of the collection is clearly seen against the lumen of the gastrointestinal tract. There are several techniques that can be employed to successfully drain the collection endoscopically. The two

most current main techniques involve the placement of multiple plastic pigtail stents or the placement of a double lumen-apposing stent to establish a connection between the WOPN and the lumen of the gastrointestinal tract for drainage. If multiple plastic pigtail stents are to be deployed, a wire is advanced into the cavity, and the tract is serially dilated with balloon dilators to open a cystenterostomy or cystogastrostomy through which multiple plastic pigtail stents can be placed to maintain patency. If a double lumen-apposing stent is placed, there are two possible approaches with both a cold and hot delivery system. With a cold delivery system, a wire is placed into the cavity, and the tract is dilated with balloon dilators until the stent delivery catheter can pass through the opening at which point the inner flange of the metal stent can be deployed followed by the outer flange to directly connect the cavity to the lumen. With a hot delivery system, the catheter tip is connected to cautery and can directly puncture into the pancreatic collection at which point the stent can be deployed. Following double lumen-apposing stent deployment, the lumen of the stent can be dilated using a balloon dilator to establish drainage. Direct comparisons of these two techniques are limited, but available retrospective data would suggest superiority of the metal stent approach. A retrospective look at a total of 70 patients showed similar efficacy rates between the two approaches, but suggested superiority in terms of reduced procedure time for the metal stent method [7]. Another more recent retrospective study of 61 patients undergoing multiple plastic stent placement vs. 72 patients undergoing a double lumen-apposing stent approach suggested fewer direct endoscopic necrosectomy sessions, fewer adverse events, less need for salvage surgery, and significantly shorter hospital stay as well as higher overall success rate for those undergoing metal stent placement when compared to multiple plastic stents with the limitations inherent to a retrospective study [8].

Although most data on endoscopic necrosectomy is based on older techniques, it is clear that regardless of the technique chosen, the less invasive endoscopic approach is superior to

surgical methods. A recent systematic review demonstrated that endoscopic methods for necrosectomy led to an 81% clinical success rate in resolving WOPN, mortality of 6%, and complications in 36% of patients with the most frequent complication being bleeding [9]. The lumen-apposing metal stent approach described above is the newest technique for WOPN management, and the most recent data gathered using this method was collected in a retrospective multicenter study of 124 patients demonstrating clinical success in 86% of patients after 3-month follow-up. In this cohort, only 13 patients required a percutaneous drain, and three required surgical interventions [10].

Outcome

This patient ultimately underwent endoscopic necrosectomy performed under endoscopic ultrasound guidance using a transgastric approach for placement of a double lumen-apposing metal stent with immediate decompression of the cavity through drainage of copious amounts of fluid and necrotic debris. He experienced near-instantaneous relief of his abdominal pain and began taking oral nutrition shortly after the index procedure. He was weaned off of total parenteral nutrition. Subsequent imaging demonstrated significant interval decrease in the size of his collection following the procedure. A repeat endoscopy was performed a couple weeks after stent placement at which point endoscopic debridement took place through the previously placed double lumen-apposing metal stent. He tolerated the debridement well, and follow-up imaging demonstrated near-complete resolution of the collection. Subsequent repeat endoscopy was then performed to remove the metal stent, and he ultimately did very well with complete resolution of his symptoms with no need for any further procedures. Understanding the proper approach to management of WOPN saved this patient from an invasive procedure associated with significant morbidity and mortality.

Clinical Pearls/Pitfalls

- When prescribing the rate of intravenous fluid resuscitation, do not forget to take into account all fluid losses, including diarrhea.
- Proper, aggressive intravenous resuscitation is key to start as early as possible during the treatment of an acute bout of pancreatitis to minimize pancreatic necrosis and improve survival.
- Perform a thorough work-up to determine the etiology of acute pancreatitis.
- Use a scoring system such as the BISAP score, Glasgow criteria, or Ranson's score to predict the severity of pancreatitis.
- In cases with minimally symptomatic WOPN, expectant management with watchful waiting can lead to resolution in about 60% of cases.
- Despite increased invasiveness and higher morbidity and mortality associated with surgical drainage of WOPN, it may be the treatment of choice in areas where less invasive approaches are not available or as step-up therapy in cases that are refractory to endoscopic or percutaneous drainage.
- Percutaneous drainage of WOPN can serve as standalone therapy in some cases but is most often used to decompress retroperitoneal collections that may not be amenable to endoscopic therapy or to stabilize patients prior to an endoscopic or surgical approach.
- When appropriate expertise is available, endoscopic drainage of WOPN offers the highest degree of success and lowest rate of complications compared with other management options for WOPN.

References

1. Vitas GJ, Sarr MG. Selected management of pancreatic pseudocysts: operative versus expectant management. Surgery. 1992;111(2):123.
2. Yeo CJ, Bastidas JA, Lynch-Nyhan A, et al. The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet. 1990;170(5):411.
3. Rasch S, Reichel S, Rau B, et al. Open surgical versus minimal invasive necrosectomy of the pancreas - a retrospective multicenter analysis of the German Pancreatitis Study Group. PLoS One. 2016;11(9):e0163651.
4. Freeny PC, Hauptmann E, Althaus SJ, et al. Percutaneous DT-guided catheter drainage of infected acute necrotizing Pancreatitis: techniques and results. AJR Am J Roentgenol. 1998;170(4):969.
5. Mortele KJ, Girshman J, Szejnfeld D, et al. CT-guided percutaneous catheter drainage of acute necrotizing Pancreatitis: clinical experience and observations in patients with sterile and infected necrosis. AJR Am J Roentgenol. 2009;192(1):110.
6. Adams DB, Anderson MC. Percutaneous catheter drainage compared with internal drainage in the management of pancreatic pseudocyst. Ann Surg. 1992;215(6):571.
7. Mukai S, Itoi T, Baron TH, et al. Endoscopic ultrasound-guided placement of plastic vs. biflanged metal stents for therapy of walled-off necrosis: a retrospective single-center series. Endoscopy. 2015;47(1):47–55.
8. Bapaye A, Dubale NA, Sheth KA, et al. Endoscopic ultrasonography-guided transmural drainage of walled-off pancreatic necrosis: comparison between a specially designed fully covered bi-flanged metal stent and multiple plastic stents. Dig Endosc. 2017;29(1):104–10.
9. van Brunschot S, Fockens P, Bakker OJ, et al. Endoscopic transluminal necrosectomy in necrotizing pancreatitis: a systematic review. Surg Endosc. 2014;28(5):1425–38.
10. Sharaiha RZ, Tyberg A, Khashab MA, et al. Endoscopic therapy with lumen-apposing metal stents is safe and effective for patients with pancreatic walled-off necrosis. Clin Gastroenterol Hepatol. 2016;14(12):1797–803.

Chapter 9
Autoimmune Pancreatitis

Anuradha Madhavan and Timothy B. Gardner

Case Study

A 68-year-old man presents to the ED for expedited workup of jaundice. He has been feeling weak and fatigued with very low energy levels for 3–4 weeks in which time he has a reported weight loss of 22 lb and anorexia. He did not report any pain, bleeding, and changes in bowel habits at this time. His PMH is significant for rheumatoid arthritis. He quit smoking and drinking over 10 years ago. On physical exam, he appears mildly icteric and labs showed elevated LFTs, CA 19-9, and IgG4. A CT scan demonstrated a sausage-shaped pancreas with relatively homogeneous parenchymal enhancement. See Fig. 9.1. There was no focal lesion and a minimal nonspecific pancreatic ductal dilatation was identified.

A. Madhavan (✉)
Section of Gastroenterology and Hepatology,
Dartmouth-Hitchcock Medical Center,
One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: anuradha.madhavan.med@dartmouth.edu

T.B. Gardner, MD
Section of Gastroenterology and Hepatology,
Dartmouth-Hitchcock Medical Center,
One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.b.gardner@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_9,

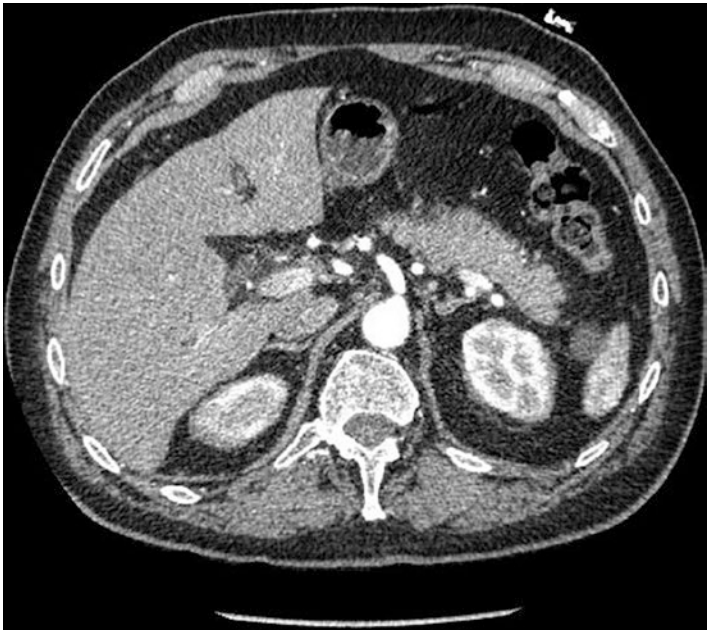

Figure 9.1 CT scan demonstrating the classic sausage-shaped appearance of patients with type 1 AIP

My Management

1. Serologic testing for IgG4 and CA 19-9 and CT imaging for evaluation of autoimmune pancreatitis
2. Glucocorticoid treatment over 12 weeks with taper beginning after 4 weeks.

Diagnosis and Assessment

Autoimmune pancreatitis (AIP) was initially recognized as a disease that primarily affects the pancreas with some ability to spread to other organs. More recently, there has been increasing recognition of the systemic association of AIP with a number of autoimmune conditions [1].

AIP can now be classified into type 1 and type 2, each presenting a distinct clinical profile. In type 1 AIP, the pancreas is a part of a systemic IgG4-positive disease, also known as lymphoplasmacytic sclerosing pancreatitis (LPSP). Type 1 AIP is a rare disease which is more prevalent in men, and typical patients are between ages 60 and 65 [2]. Diagnosis of type 1 AIP can follow several criteria—radiological, serological, histological, and clinical—that have been established internationally over time. Notable among these are the HISORt (*h*istology, *i*maging, *s*erology, *o*ther organ involvement, and *r*esponse to *t*herapy) criteria established by the Mayo clinic [3] and the more recent International Consensus Diagnostic Criteria (ICDC) guidelines [4].

The five features of the ICDC guidelines are similar to the criteria used in HISORt and include (1) pancreatic imaging of either the parenchyma or ducts, (2) serology, (3) other organ involvement (OOI), (4) histology of the pancreas, and (5) response to corticosteroid therapy. It is notable that type 1 AIP can be further classified into typical and atypical patterns based on the ICDC guidelines. While the typical pattern completely follows established ICDC guidelines, these criteria are not met in atypical type 1 AIP. For completing the diagnosis of atypical type 1 AIP, there is a requirement for an endoscopic pancreatogram and pancreatic biopsy.

Significant observations in type 1 AIP are diffuse enlargement of the pancreatic parenchyma on CT scan [5]. This is otherwise also visualized as a sausage-like pancreas. On endoscopic retrograde cholangiopancreatography (ERCP), one might observe long strictures or multiple strictures of the pancreatic duct [6]. IgG4 serum levels in type 1 AIP can be up to ten times the upper limit of IgG4 values [5]. Histologic findings can include marked lymphoplasmacytic infiltration with fibrosis (without granulocytic infiltration), storiform fibrosis, obliterative phlebitis, and abundant (>10 cells/HPF) IgG4-positive cells [5].

Type 2 AIP is of idiopathic origin and manifests as a duct-centric pancreatitis. Patients with type 2 AIP tend to be younger (aged 45–48), and there is an equal distribution across gender [7]. Serologic changes in IgG4 are absent in type 2 AIP. In

addition, the pathology of type 2 AIP is idiopathic and restricted to the pancreas (head and distal portion of the bile duct) with no demonstrable extra-pancreatic involvement. Histologically, type 2 AIP is associated with granulocytic epithelial lesions (GELs). However, GELs are likely to be present in 27% of type 1 AIP cases [8]. In addition, due to the lack of OOI and IgG4 in type 2 AIP, which indicates a systemic autoimmune process, there is a need for pancreatic biopsy to rule out pancreatic cancer prior to establishing the diagnosis of AIP [9].

The classic clinical presentation of the AIPs involves obstructive jaundice, abdominal pain, and acute pancreatitis [7]. Obstructive jaundice is a common presenting symptom, more so in type 1 than in type 2 AIP. Thus, patients may require the placement of a biliary stent while they await diagnostic confirmation for alleviation of the symptoms. Abdominal pain experienced in AIP is mild and may or may not be accompanied by attacks of abdominal pain from acute pancreatitis. In the later stages, patients with AIP may develop severe exocrine and endocrine insufficiency [10]. In addition, untreated type 1 AIP can manifest as systemic inflammation showing sclerosing cholangitis, thyroiditis, lymphadenopathy, sialadenitis, and retroperitoneal fibrosis [11].

The presenting symptoms in AIP are largely similar to those that manifest in pancreatic adenocarcinoma. It is essential to rule out adenocarcinoma and multiple tests can be used to this end. CA 19-9 levels can be elevated in AIP and in pancreatic adenocarcinoma due to bile duct obstruction. However, the levels of CA 19-9 should drop with a trial of steroids for the treatment of AIP. CA 19-9 levels that continue to rise are a red flag for the presence of a pancreatic cancer [12]. A FNA or core biopsy of the pancreas could yield some evidence, and surgical resection is necessary for confirmation.

Management

The management of AIP involves the oral administration of glucocorticoids (prednisone and prednisolone are commonly used). The standard dose of corticosteroids to be

given for AIP is 40 mg of prednisone for 4 weeks. A reassessment of imaging and laboratory work is recommended after 2 weeks. Tapering of the corticosteroids can be done at the rate of 5 mg/day every week for 8 weeks. Successful treatment involves the resolution of clinical symptoms and downward trending of CA 19-9, IgG4, and liver function tests.

A large percentage of patients (31% in type 1 and 9% in type 2 [13]) can relapse after steroid discontinuation, and factors that govern the relapse include high levels of IgG4 at the time of diagnosis. On relapse, patients may receive a 12-week course of oral steroids along with immunomodulator therapy.

Immunomodulator agents (azathioprine, 6-mercaptopurine, mycophenolate mofetil) have been used in patients following relapse from steroid withdrawal and those who fail steroid trial or do not tolerate steroids. Azathioprine (2 mg/kg/day), 6-MP (1 mg/kg/day), and mycophenolate mofetil (750–1000 mg BID) were most commonly used in that order of preference for up to 2 years [14]. More recently, a few infusions of rituximab (anti-CD20 monoclonal antibody) have been found to be useful in treating a patient with refractory AIP [15].

Outcome

A biliary stent was placed during the ERCP in the patient for management of the obstructive jaundice. In addition, a biliary stricture was identified on ERCP; however, no mass was found to be present on endoscopic ultrasound. Taken together with the elevated IgG4, the initial treatment for the patient was to start him on prednisone 40 mg daily for 4 weeks. The patient had an excellent response to the prednisone with complete resolution of the inflammatory changes around the pancreas on CT scan and a downtrending of the IgG4 and CA 19-9. See Fig. 9.2. Based on this evidence and treatment response, the diagnosis was confirmed to be type 1 AIP, and the prednisone taper was initiated.

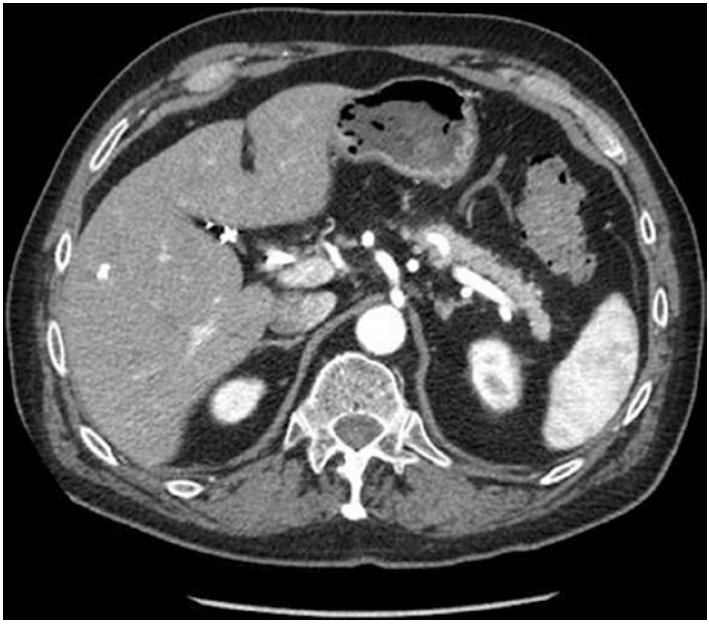

FIGURE 9.2 CT scan demonstrating regression of the inflammatory changes in the patient after treatment with corticosteroids

Clinical Pearls/Pitfalls

- Type 1 AIP is a systemic disease, more common in males age >50, with a demonstrable elevation in IgG4 and sausage-shaped pancreas on CT imaging. Response to corticosteroids can provide both treatment and diagnostic confirmation.
- Type 2 AIP arises in younger individuals of either gender and follows an idiopathic duct-centric process with localized pancreatic involvement requiring a biopsy for diagnostic confirmation.
- The triad of clinical presentation of AIP—obstructive jaundice, abdominal pain, and acute pancreatitis—

raises suspicion for a pancreatic adenocarcinoma which can be ruled out with a biopsy in the absence of a response to corticosteroids.
- Corticosteroids (at 40 mg) can be initiated for 4 weeks followed by an 8-week taper of 5 mg/week after normalization of imaging, IgG4, and CA 19-9.
- CA 19-9, while expected to be elevated in AIP, could also be indicative of malignancy, and a downtrending with treatment is the expected response.

References

1. Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol. 2003;98:2811–2.
2. Frey CF, Zhou H, Harvey DJ, et al. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994–2001. Pancreas. 2006;33:336–44.
3. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol 2006;4:1010–6; quiz 934.
4. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–8.
5. Chari ST, Takahashi N, Levy MJ, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009;7:1097–103.
6. Horiuchi A, Kawa S, Hamano H, et al. ERCP features in 27 patients with autoimmune pancreatitis. Gastrointest Endosc. 2002;55:494–9.
7. Kamisawa T, Chari ST, Giday SA, et al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas. 2011;40:809–14.
8. Sumimoto K, Uchida K, Mitsuyama T, et al. A proposal of a diagnostic algorithm with validation of International Consensus Diagnostic Criteria for autoimmune pancreatitis in a Japanese cohort. Pancreatology. 2013;13:230–7.

9. Kanno A, Ishida K, Hamada S, et al. Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. Gastrointest Endosc. 2012;76:594–602.
10. Ikeura T, Miyoshi H, Shimatani M, et al. Long-term outcomes of autoimmune pancreatitis. World J Gastroenterol. 2016;22:7760–6.
11. Okazaki K, Uchida K. Autoimmune pancreatitis: the past, present, and future. Pancreas. 2015;44:1006–16.
12. van Heerde MJ, Buijs J, Hansen BE, et al. Serum level of Ca 19-9 increases ability of IgG4 test to distinguish patients with autoimmune pancreatitis from those with pancreatic carcinoma. Dig Dis Sci. 2014;59:1322–9.
13. Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut. 2013;62:1771–6.
14. Hart PA, Topazian MD, Witzig TE, et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. Gut. 2013;62:1607–15.
15. Topazian M, Witzig TE, Smyrk TC, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2008;6:364–6.

Chapter 10
Diagnosis and Screening for Pancreatic Malignancy

Nigeen H. Janisch

Case Study

A 53-year-old diabetic male presents complaining of yellow skin and diffuse pruritus for the past 2 weeks. AST and ALT are within normal limits while total bilirubin is elevated at 9.4. All other labs show no abnormalities. CT of the abdomen and pelvis with IV contrast shows an irregular mass at the head of the pancreas but is unable to characterize it further (Fig. 10.1). The mass was suspicious for pancreatic malignancy given location and presenting symptoms but must be further assessed with another imaging modality as well as tissue sampling. An endoscopic ultrasound with fine-needle aspiration (EUS-FNA) is scheduled for the next morning.

My Management

A. Continue with the above plan of obtaining an EUS-FNA for cytology of mass.

N.H. Janisch, MD
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Nigeen.H.Janisch@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_10,

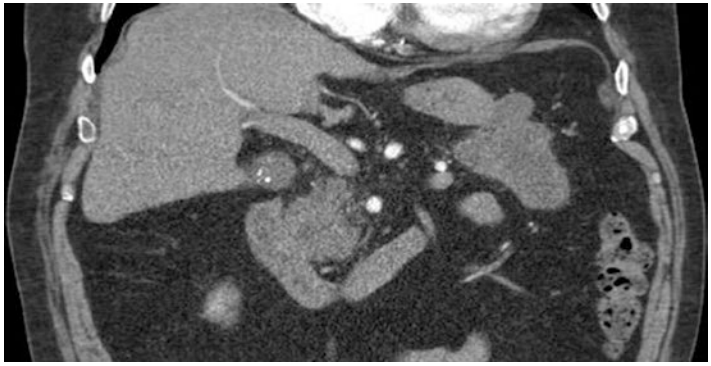

Figure 10.1 CT demonstrating mass in the pancreatic head

B. Further imaging required with CT angiography to determine if surgery is appropriate.
C. Consult with surgery for possible Whipple procedure and definite pathology.
D. Obtain CA 19-9 and CEA for baseline levels prior to therapeutic treatment.

Diagnosis and Assessment

Around 75% of pancreatic cancers occur in the head or neck of the pancreas, with about 15–20% in the body and 5–10% in the tail. Because the majority of tumors arise in the head and neck area, the most characteristic sign of pancreatic cancer is painless jaundice. Usually, patients will first notice changes in stool color, darkening of urine, and some pruritus before their jaundice reaches the point where it is clinically recognizable, which does not occur until total bilirubin reaches 2.5–3 mg% [1]. This patient presented with fairly classical symptoms; however, the difficulty of diagnosing pancreatic cancer purely based on presentation lies in the overlap it has with many more common conditions—such as gallbladder pathology or liver disease.

The clinical presentation of pancreatic cancer may be extremely nonspecific and subtle with early diagnosis particularly difficult. Some other common signs of clinical presentation include anorexia with or without weight loss, malaise, nausea, and midepigastric or back pain. Weight loss can be related to the cancer-associated anorexia but can also be malabsorption from pancreatic exocrine insufficiency [2]. The latter may also present with diarrhea and greasy, malodorous stools.

New-onset diabetes mellitus can sometimes be associated with pancreatic adenocarcinoma, which has prompted discussion on whether this may be a manifestation of the disease and possible clue to early presentation. However, only about 1% of those with new-onset diabetes develop pancreatic cancer, making preventative screening inefficient and ineffective [3]. It is recommended to consider pancreatic cancer in patients with diabetes associated with unusual weight loss and abdominal problems, but there are currently no specific recommendations for imaging or lab tests. Given that the majority of presentations occur as such an advanced stage, early detection will have to be done in asymptomatic individuals. Further study needs to be performed on the role of hyperglycemia and new-onset diabetes in relation to the detection of early stage pancreatic cancer [4, 5].

Currently, the primary form of assessment in a patient suspected of pancreatic cancer is cross-sectional imaging. The most common forms used are CT, endoscopic ultrasound (EUS), MRI, endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRCP). The decision on which to proceed with depends on the need for ongoing characterization of the pancreatic mass and surrounding organs, obtaining tissue samples for cytologic evaluation, and the possibility for therapeutic intervention if there is obstruction present [6]. CT angiography with pancreas-specific protocol is recommended for patients who do not show signs of distant metastases on initial CT. This type of imaging is used to evaluate the vascular system in relation to the pancreatic mass as this is an

important factor when determining the feasibility of surgical resection [7]. EUS, if done by an expert, has been shown to be the most sensitive and specific imaging technique for the detection of pancreatic cancer. In addition, it provides the option of a fine-needle aspiration as a relatively noninvasive way to sample tissue for a more definitive diagnosis [8]. Though imaging remains one of the primary tools in initial diagnosis, it may be difficult to differentiate a pancreatic cancer in a patient with chronic pancreatitis where both imaging and tumor markers may have similar abnormalities [9].

Management

Given the results of the CT scan on this patient, it was determined that histologic categorization of the mass would be an appropriate next step; therefore, EUS with FNA was scheduled. While cytologic results of benign or malignant are fairly straightforward, there is some debate as to the interpretation of the "indeterminate" results—atypical and suspicious. Often, they can lead to repeat procedures and an ill-defined course of therapy, which can delay potentially life-saving treatments in the case of pancreatic cancer, which has the lowest 5-year survival rate among recalcitrant cancers at 6% [8]. Lethality of the disease is credited to the inability to detect it in the early stages as most pancreatic cancer becomes clinically visible as a late-stage disease. Rapid growth and spread throughout the body are also a barrier to cure. Surgery is currently the only treatment proven to improve that survival rate, though only about 20% of patients qualify for surgical resection given that the disease usually presents at advanced stages [10].

Tumor markers have also become a fairly effective way to track tumor activity. CA 19-9, an oligosaccharide that is found on circulating mucins, is the tumor marker most readily associated with pancreatic cancer. It is native to the biliary tract and can be elevated in some acute or chronic biliary diseases. Of patients with pancreatic cancer, about 75–85%

have an elevated CA 19-9 [11]. Unfortunately, levels of the antigen do not rise to clinically significant levels until the cancer moves into later stages. For this reason, it is not currently used as a regular screening tool. CA 19-9 serves more of a role in the staging the tumor growth as well as measuring follow-up response to surgical, chemotherapeutic, or radiotherapeutic treatments. A CA 19-9 greater than 100 U/mL is highly specific for pancreatic malignancy in the absence of other biliary obstruction, liver, or pancreatic disease [11].

CEA, another tumor marker usually associated with other gastrointestinal malignancies, can also be elevated in 40–45% of patients with pancreatic cancer. This antigen, a glycoprotein arising from fetal tissue, is neither sensitive nor specific for pancreatic cancer but may also be used as a measurement of response in addition to CA 19-9 [12].

Outcome

Our patient tolerated the EUS with FNA well, and the samples were sent to pathology for histologic evaluation. The results read suspicious, and further imaging did not reveal any signs of metastasis to nearby organs. The EUS report showed the tumor to be about 3 cm and located in the head of the pancreas, obstructing the biliary tree. This would explain the patient's presenting symptoms and initial lab abnormalities. CA 19-9 at this time was 142 and CEA was 35. After some discussion, it was thought that this cytologic result of suspicious was more likely to be malignant than benign given the location of the mass and the elevated CA 19-9. Literature review also revealed some data showing that around 90–95% of suspicious cytologic results may ultimately be malignant on final surgical pathology [8]. Given this clinical picture and supporting information, it was decided to proceed with initial surgical resection with the goal of a cure. Chemotherapy and radiation would be discussed following the procedure and dependent upon the tissue pathology obtained.

Clinical Pearls/Pitfalls

- Common presentations include painless obstructive jaundice, anorexia with or without weight loss, malaise, nausea, and midepigastric or back pain.
- Labs may show abnormalities in AST, ALT, and total bilirubin but also may be within normal limits.
- Imaging most highly recommended are CT and EUS with or without FNA for histology.
- There are no current recommendations for preventative screening of pancreatic cancer.
- Keep pancreatic cancer in the differential for a patient with new-onset diabetes associated with unusual symptoms.
- CA 19-9 and CEA are tumor markers associated with pancreatic cancer that can be used to track tumor progression and/or response to treatment if elevated at the time of diagnosis.
- Diagnosis may be even more difficult in those with chronic pancreatitis as imaging and tumor markers may not be abnormal in both.
- Surgical resection is currently the only treatment that improved 5-year survival rate.

References

1. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol. 2009;6(12):699–708.
2. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:1039–49.
3. Chari S, Leibson C, et al. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology. 2005;129(2):504–11.
4. Canto M, Wroblewski L, Goggins M, Petersen G, Brune K, Yea C, Giardello F, Hruban R. Screening for pancreatic neoplasia in high-risk individuals. Gastroenterology. 2002;122:A-17.

5. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer (a meta-analysis). JAMA. 1995;273:1605–9.
6. Yoshinaga S, Suzuki H, Oda I, Saito Y. Role of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for diagnosis of solid pancreatic masses. Dig Endosc. 2011;23(Suppl 1):29–33.
7. Al-Hawary MM, Francis IR, Chari ST. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology. 2014;270(1):248–60.
8. Turner BG, Cizginer S, Agarwal D, et al. Diagnosis of pancreatic neoplasia with EUS and FNA: a report of accuracy. Gastrointest Endosc. 2010;71(1):91–8.
9. Karasawa E, Goldberg HI, Moss AA, et al. CT pancreatogram in carcinoma of the pancreas and chronic pancreatitis. Radiology. 1983;148(2):489–93.
10. Chari S, Kelly K, et al. Early Detection of sporadic pancreatic cancer: summative review. Pancreas. 2015;44(5):693–712.
11. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313–27.
12. Fujioka S, Misawa T, Okamoto T, Gocho T, Futagawa Y, Ishida Y, et al. Preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the evaluation of curability and resectability in patients with pancreatic adenocarcinoma. J Hepatobiliary Pancreat Surg. 2007;14(6):539–44.

Chapter 11
Hereditary Pancreatic Cancer

Lisa Yoo and John M. Levenick

Case Study

A 50-year-old man was referred from his primary care physician for a long history of abdominal pain, weight loss, and bloating. There was no history of diarrhea, constipation, vomiting, and/or gastrointestinal bleeding, and family history was negative for colonic polyps or colon cancer. He has only history as a child of intussusception. Physical examination was normal except for the presence of well-demarcated, blue-black to dark-brown pigmented maculae which were noted on the perioral, perinasal, and periocular skin and lower lip. No abdominal tenderness, masses, infiltration, or organomegaly were appreciated. Due to high suspicion of Peutz-Jeghers syndrome, the patient underwent colonoscopy and esophagogastroduodenoscopy, a capsule

L. Yoo, DO • J.M. Levenick, MD (✉)
Department of Gastroenterology and Hepatology,
Penn State, Milton S. Hershey Medical Center,
500 University Dr, Hershey, PA 17033, USA
e-mail: jlevenick@hmc.psu.edu

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_11,

endoscopy, and testicular exam. A computerized tomography (CT) scan was normal.

My Management

A. I agree with the management above and will screen every 3 years with esophagogastroduodenoscopy (EGD), colonoscopy, and capsule endoscopy.
B. Perform endoscopic ultrasound for pancreatic cancer surveillance in addition to above testing with surveillance every 2 years and alternating with magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP).

Diagnosis and Assessment

Pancreatic cancer (PC) is the fourth most common cause of death from cancer among adults in the USA as well as one of the top ten cancer killers in Europe and industrialized countries [1–3]. An estimated 49,000 diagnoses and 38,000 deaths from pancreatic duct adenocarcinoma (PDAC) occurred in 2013 in the USA [3]. Eighty-five to 90% of patients present with disease that is not resectable (i.e., locally advanced or metastatic disease) at the time of diagnosis with a 3.5-month median survival for non-resected patients [1, 3]. In average-risk people, the lifetime risk of developing PC is 1 in 67 (1.49%) which increases with age with the mean age at diagnosis of 71 years [3]. Certain groups, such as those with hereditary pancreatitis or a family history of PC, have increased risk to develop PC, especially at an early age. Patients with hereditary pancreatitis are at a substantially increased risk of developing PDAC [1]. The average age of diagnosis of pancreatic cancer is 68 years in familial PC with the increased risk apparently beginning at about the age of 40 [1, 3].

Hereditary Causes of Pancreatic Ductal Adenocarcinoma (PDAC)

Established risk factors for PDAC constitute both environmental and inherited influences, which include ABO blood group, history of chronic pancreatitis, and a family history of pancreatic cancer [4]. Modifiable risk factors for increasing PC risk include tobacco exposure, alcohol use, diet, obesity, diabetes mellitus, as well as certain abdominal surgeries and infections [3].

Approximately 5–10% of PDAC have a hereditary component, with 20% of these cases implicating a specific germline mutation [3, 5]. The underlying genetic basis of PC predisposition has been identified in less than 20% of such families, although 50–80% of families demonstrate an autosomal-dominant inheritance pattern [4]. An inherited predisposition to PC manifests in three settings:

1. Familial pancreatic cancer (FPC) which is defined as a kindred in which at least two first-degree relatives (FDRs) have PC that otherwise does not fulfill the diagnostic criteria for an inherited cancer syndrome
2. Hereditary pancreatitis
3. Hereditary tumor predisposition syndromes, accounting for 15–20% of the burden of inherited diseases such as hereditary breast-ovarian cancer (HBOC), Lynch syndrome (HNPCC), familial atypical multiple mole melanoma syndrome (FAMMM), cystic fibrosis, and ataxia-telangiectasia (AT), familial adenomatous polyposis (FAP), and Peutz-Jeghers syndrome (PJS) [4].

These genetic conditions have been shown to raise the risk of PC from 2 to 132-fold [3]. The presence of PC in a family increases PC risk for relatives regardless of the known gene mutation [5]. The main tool used to quantify PC risk is still family history; risk stratification is determined from the number of affected family members and the relationships among at-risk individuals [2].

Familial Pancreatic Cancer

Familial pancreatic cancer (FPC) is defined as a family with at least two first-degree relatives (FDRs), meaning a parent-child or sibling pair, with PC without an identifiable syndrome or genetic cause within the family [5]. Relatives are stratified dependent on relationships to the affected relatives; an individual with three or more FDR with PC in a family meeting the FPC definition carries a 17 relative risk (RR) [5]. PC risk is estimated to be 6.4-fold greater in individuals with two FDRs with PC (lifetime risk 8–12%) and 32-fold greater in individuals with three or more FDRs with PC (lifetime risk 40%) [6]. Among kindreds with familial PC, risk is higher in those with a young-onset PC (age <50 years, RR, 9.3) compared with those without [7]. A 2009 meta-analysis demonstrated that having just one affected relative resulted in an 80% increased relative risk of developing PC [3]. Still, there is no consensus on whether to screen individuals without an affected FDR, including individuals with a young-onset PC relative or patients with new-onset diabetes [2]. Nevertheless, recognition of individuals at increased risk of having genetic mutations may aid in defining patients that will benefit from early detection of these pancreatic neoplasms, as well as targeted, gene-specific therapy [3].

Familial pancreatic cancer (FPC) is responsible for approximately 80% of PC with a genetic basis [3]. Among FPC kindreds, having two or three FDRs with PC was associated with a 6.4-fold and 32-fold greater risk of developing PC, respectively [3]. Additionally, studies of the European Registry of Hereditary Pancreatitis and FPC as well as the German national case collection for FPC registries have described anticipation, meaning developing PC roughly 10 years earlier than their affected parent, in 59–80% of over 100 FPC families [3]. Segregation analyses have shown evidence for a yet unidentified autosomal-dominant, high-risk allele influencing PC onset age present in 7 of 1000 individuals [3]. The *palladin* gene, a proto-oncogene overexpressed in some sporadic pancreatic tumors, has been found to be mutated in affected

members of one PC family [3]. This gene codes for a cytoskeleton protein that promotes tumor invasion in fibroblasts [3]. The occurrence of multiple primary malignancies in FPC kindreds suggests an underlying genetic predisposition, with variable penetrance, interaction with other modifier alleles, and gene-environment factors [4].

Hereditary Pancreatitis

Hereditary pancreatitis (HP) is rare but is the only known inherited cancer predisposition syndrome for which PC is the sole cancer risk factor [5]. Hereditary pancreatic cancer is defined as a genetic syndrome with an identifiable gene mutation associated with an increased PC [5]. HP is an inherited form of chronic pancreatitis, where a subset of families carry gain-of-function mutations in *PRSS1*, which codes for a cationic trypsinogen digestive enzyme, with a penetrance estimated at 80% [5]. The *SPINK1* gene codes for a serine protease inhibitor that inhibits active trypsin; mutations in this gene also have associations with various forms of pancreatic disease, including pancreatitis [3]. Typically, HP is characterized by recurrent attacks of acute pancreatitis starting in the first to second decade of life and can lead to pancreatic failure, diabetes, and PC risk ranging from 18% to 53% [3, 5, 8]. A 2010 meta-analysis found a relative risk of 69 for PC for patients with HP compared to the general population [3]. PC surveillance is challenging in HP patients as there is gross distortion of the pancreatic architecture by chronic pancreatitis [5]. An option for high-risk patients is total pancreatectomy, with or without islet autotransplantation (TPIAT) [5]. There is an increased risk in patients who smoke and have diabetes [5]. Some large HP families have never had a case of PC, and caution is required prior to recommending surgery [5].

Homozygous mutations in the autosomal recessive *CFTR* gene cause cystic fibrosis, which is associated with both a younger age of onset (median age of 35) and 5.3-fold increased risk of PC development [3]. However, even when

a *CFTR* gene mutation is inherited in heterozygous fashion, a fourfold greater chance of developing chronic pancreatitis has been shown [3].

Hereditary Tumor Predisposition Syndromes

Germline mutations, in the *BRCA2*, *PALB2*, *p16*, *STK11*, *ATM*, and *PRSS1* genes and the hereditary colon cancer genes, are associated with significantly increased risk of PC but explain only approximately 10% of the familial susceptibility to PC [2]. Individuals with PC susceptibility gene mutations may not have many affected family members; thus, patients with apparent sporadic PC can have *BRCA2* mutations, as can those without a family history of breast or ovarian cancer [2]. Incomplete or low penetrance is a common feature of familial PC susceptibility gene mutations [2].

Patients with Peutz-Jeghers syndrome (PJS) have shown the greatest defined inherited risk factor for PC [5]. These patients present with mucocutaneous hyperpigmentation and hamartomatous polyposis who generally carry germline *STK11* gene mutations have a 132-fold risk of PC with a lifetime risk at age 65–70 of 11–36% [5, 9, 10]. Diagnosis of PJS requires the presence of any one of the following:

1. Two or more histologically confirmed PJS polyps
2. Any number of PJS polyps detected in an individual who has a family history of PJS in a close relative
3. Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative
4. Any number of PJS polyps in an individual who also has characteristic mucocutaneous pigmentation [11].

Individuals who meet clinical criteria for PJS should undergo genetic testing for a germline mutation in the *STK11* gene. Approximately 96% PJS patients have *STK11* gene mutation [11]. Genetic testing in an individual who meets clinical criteria for PJS serves to confirm the diagnosis of PJS and counsel at-risk family members. However, not all mutations

associated with PJS have been identified [12]. Thus, if no pathogenic *STK11* mutation is found in an individual who meets clinical criteria for PJS and there is no known mutation of PJS in the family, the diagnosis of PJS is not excluded. Such individuals and their at-risk relatives still require frequent endoscopic surveillance for removal of polyps throughout the gastrointestinal tract and screening for extraintestinal cancers [12]. Otherwise, if genetic testing is performed and a mutation is found in an affected individual, then genetic testing of at-risk relatives will provide true positive or negative test results [12]. At-risk patients who receive true negative test results have a risk of cancer similar to that of the general population [12]. At-risk relatives who test positive should follow the surveillance guidelines for individuals with PJS [12].

Hereditary breast-ovarian cancer syndrome (HBOC) is an autosomal dominant disorder with increased risks for breast cancer (47–55% by age 70), ovarian cancer (17–39%), and other cancers including prostate, male breast, melanoma, and PC [5]. Cancer diagnoses present in multiple family generations often diagnosed prior to age 50, with the incidence in the general population being 1 in 500 individuals [5, 13]. Carrier frequency is increased among Ashkenazi (Eastern European) Jewish ethnicity, with 1 in 40 individuals at risk [5]. The majority of HBOC cases are due to mutations in the *BRCA1* or *BRCA 2* genes [5]. There are three founder mutations in this population: 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2* [5]. In *BRCA1* mutation carriers, there is a relative risk of 2.8% compared to the general population risk of 1.3% [14]. *BRCA2* mutations have a 3.5 relative risk compared to non-mutation carriers (5–7% lifetime risk) for developing PC [5]. *BRCA1* mutation carriers have a relatively small risk of PC; as such, PC surveillance does not warrant inclusion of these at-risk patients. However, with the higher risk with *BRCA2*, these patients warrant consideration for surveillance which will be discussed.

The localizer of *BRCA2* (*PALB2*) gene was originally identified as a breast cancer susceptibility gene associated with the Fanconi anemia DNA repair pathway (FANCN) [5].

Analysis of *PALB2* in *BRCA*-negative families identified a sixfold increased risk for PC in relatives of the mutation carrier [15]. Recommendations for surveillance in these patients have not been established, but individuals from familial pancreatic cancer kindred should be counseled according to the familial pancreatic cancer risk, with greater assumed risk if *PALB2* is identified with cancer in the family [5].

Ataxia-telangiectasia (AT) is a rare autosomal recessive condition characterized by early-onset progressive cerebellar ataxia, skin telangiectasias, ionizing radiation sensitivity, and immunodeficiency [5]. The ATM gene is affected [5]. AT presents during the first decade of life in biallelic mutation carriers [5]. Mono-allelic mutation carriers harbor cancer risks including the pancreas and breast [5]. In a recent analysis of 166 unrelated familial pancreatic cancer patients, 2.4% were identified as *ATM* mutation carriers; 4.6% of these patients carried an ATM mutation if there were more than three cases of PC in their relatives [13]. Genetic counseling and specific medical management are warranted for families with *ATM* mutations [5]. PC surveillance is not clearly delineated in this population, though those meeting familial pancreatic cancer definition may consider surveillance [5].

Familial atypical multiple mole melanoma syndrome (FAMMM) is an autosomal dominant disease characterized by an increased predisposition toward dysplastic nevi and early-onset melanoma [5]. *CDKN2A*, a cell cycle regulator gene coding for the p16 protein product, has functional effects in melanoma and PC cell lines, thus implicating it as a potential risk factor for inherited PC risk with an associated 17% lifetime risk for PC [5]. In a series of 120 American non-Hispanic PC cases with a family history of PC, 3.3% carried a *CDKN2A* mutation [5]. The penetrance for developing PC was estimated at 58% by age 80 for mutation carriers [5]. Recommendations include semiannual dermatology evaluations with baseline photography beginning in childhood as well as PC surveillance consideration [5]. PC risk appears to be especially high in these patients who smoke [5].

Familial adenomatous polyposis (FAP) syndrome is classically known for the plethora of early-onset gastrointestinal

adenomas [5]. This autosomal-dominant condition typically presents with symptoms by the age of 16 [5]. Inherited mutations in the tumor suppressor gene, *APC*, account for the majority of cases [5]. Although the primary cancer risk in FAP is colon cancer, extracolonic risks include duodenal, thyroid, hepatic, and the pancreas [5]. PC is observed in FAP families with higher incidence than the general population [5]. Surveillance for FAP-related cancer includes an intensive medical protocol consisting of yearly colonoscopy starting in the second decade until the presence of polyps is too numerous to remove via polypectomy [5]. Total proctocolectomy is recommended for treatment of polyps and prevention of colon cancer [5]. Esophagogastroduodenoscopy (EGD) is recommended starting by age 25 every 1–3 years or before colectomy [5]. Pancreas surveillance may be considered for such families in which PC is present [5].

Lynch syndrome accounts for 2–5% of all colorectal cancer diagnoses and is the most common cause of inherited colon cancer with a lifetime risk ranging from 52% to 82% with a mean diagnosis age of 44 [5]. Patients with Lynch syndrome have substantial increased cancer risk for colon and extracolonic tumors with a 1.3–4% lifetime PC risk [5]. PC was seen in 2 out of the 282 cancers diagnosed in a series of 121 families with known germline mutations [5]. Lynch syndrome has seen a 30-fold increased risk for PC before the age of 50 and an almost nine times likely overall risk in a cohort of 147 families [13]. Lynch syndrome tumors arise from germline mutations in mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2* [5]. Mismatch repair dysfunction results in loss of protein expression and microsatellite instability (MSI) in tumors [5].

Pancreatic Screening and Surveillance

Pancreatic cancer screening is extremely attractive if it can be detected during a curable state [2, 4]. However, the incidence of PC in the general population is low (lifetime risk 1.3%). Thus, screening is not recommended for the general

population, but selective screening is advised for high-risk individuals (HRIs) for PC based on family history or identifiable genetic predisposition (i.e., >5% lifetime risk or fivefold increased RR) [2, 4]. The risk of overtreatment for pancreatic screening is magnified by the risks of morbidity and mortality of pancreatic surgery which is approximately 1–2% [2]. No consensus guidelines exist for high-risk patients with inherited PC syndromes; as such, it is generally recommended surveillance of these patients only be performed in centers experienced in high-risk patient care and ideally enrollment into research protocols [2].

No screening protocol has yet been proven effective in any cohort at risk for PC [1]. This is due to (1) low tumor yield in all but the highest-risk cohorts (i.e., HP and hereditary pancreatic cancer); (2) the lack of tumor markers (serum, pancreatic juice, or stool) alone or in combination with sufficient sensitivity, specificity, positive predictive value, and negative predictive value to alter management independent of radiologic imaging; and (3) the assumed inefficiency of radiologic imaging techniques [e.g., multiphasic helical computed tomography (CT), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP)] in detecting tumors at a resectable stage [1].

Over the past decade, centers in the USA and Europe have initiated pancreatic screening programs with single- and multicenter cohort studies evaluating the diagnostic yield of screening (detection of asymptomatic precursor lesions and PC at baseline and follow-up) using different imaging modalities and study populations [2]. Formed in 2010, the International Cancer of the Pancreas Screening (CAPS) Consortium helped to organize global pancreatic screening [2]. In 2011, the CAPS Consortium held a multidisciplinary consensus conference with a panel of 49 experts from multiple disciplines to provide recommendations related to the following: (1) Who should be screened? (2) How should HRIs be screened and followed up? (3) When should surgery

be performed? (4) What are the goals of screening and what outcome should be?

Average-risk patients are defined as having a diagnosis of PC in one family member, diagnosed at age 55 or older; these patients do not receive screening [15]. The Consortium recommended to screen candidates with:

1. Two FDRs with PC
2. Two blood relatives with PC and at least one FDR
3. Peutz-Jeghers syndrome (PJS)
4. *BRCA2* mutation carriers with either one FDR with PC or at least two affected family members
5. *PALB2* mutation carriers with at least one FDR with PC
6. *p16* mutation carriers (FAMMM) with at least one FDR with PC
7. Lynch syndrome and one FDR with PC [3].

CAPS agreed that initial screening should include EUS and/or MRI/MRCP; however, there was no consensus about when to start or end the screening [3].

Moderate-risk patients are defined as those with two or more first-, second-, or third-degree relatives with PC or a first-degree relative (FDR) with PC diagnosed earlier than age 55 [15]. High-risk patients are defined as those with three or more first-, second-, or third-degree relatives with PC, two or more FDRs with PC, and one FDR and one second-degree relative (SDR) with PC one of whom was diagnosed before age 55 or a genetic syndrome with PC associated with it [15]. The type, frequency, and age for surveillance are not yet well defined [15]. However, surveillance for these moderate- and high-risk patients may include both EUS and MRI alternating every 2 years [15]. For all risk groups, any abnormal testing is followed by EUS if not already performed [15]. These screening recommendations are mainly based on evidence of increased risk, rather than proven screening efficacy [2]. Following screening, if no malignant or premalignant disease is identified, risk factors dictate surveillance [15]. If malignant or premalignant disease is suspected or diagnosed, surgery

must be considered [15]. Once PC is suspected on initial imaging studies, the next step in the workup is generally staging evaluation to establish disease extent and resectability. Histologic confirmation is required to establish a diagnosis of PC. This is often achieved percutaneously or via EUS.

The preferred staging system for all PC is the tumor-node-metastasis (TNM) system of the combined American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) [3]. The goal of staging is to delineate the extent of disease spread and identify those eligible for resection with curative intent [3]. An abdominal CT scan can be used but is highly dependent upon technique; a triple-phase contrast enhanced thin-slice helical CT with three-dimensional reconstruction in the preferred method to diagnose and stage PC [3]. Helical CT scanners with multiple rows of detectors permit imaging of larger volumes of tissue while acquiring both arterial and venous phases in shorter period of time [3]. This has improved the evaluation of the main pancreatic duct and detection of small tumors [3].

EUS provides a much higher resolution than transabdominal ultrasound due to the smaller distance between the echo-endoscope and the pancreas through the gastric or duodenal wall [3]. PC will appear as a hypoechoic mass, typically with dilation of the proximal pancreatic duct [3]. The lesion border may have an irregular contour, and the echo pattern of the mass may be homogenous or inhomogenous [3]. Multiple studies comparing EUS with other imaging modalities for initial diagnosis and staging of PC showed that EUS may be more accurate for smaller tumors, for local T and N staging, and for predicting vascular invasion [3]. EUS may detect metastatic disease in the liver or mediastinal lymph nodes but is inferior to CT for evaluation of distant metastases [3].

On MRI, PC can easily be visualized, but no evidence has been shown that MRI offers a significant diagnostic advantage over triple-phase CT scan for the local staging evaluation [3]. Although one potential benefit of MRI is increased sensitivity for the detection of small liver metastases compared with CT, however, the combination of CT and MRI offers little more than either alone [3].

Management

The patient underwent EUS and found no lesions highly suspicious for pancreatic cancer.

Currently, surgical resection offers the only chance of cure for PC [4]; there is no proven chemoprevention or vaccine for PC [1]. Five-year PC survival rate is dismal at 6%, largely due to diagnosis often occurring at an advanced stage [3, 5]. However, even among those who are candidates for pancreatectomy, of which 10–20% of patients undergo resection, approximately 80% still die of the disease with the median survival being 12.6 months [2–4, 16]. Often, the only cases that have a reasonable chance for a cure or prolonged survival are ones that are detected as high-risk lesions or very early (<2 cm) isolated tumors [5]. A study from the Mayo Clinic reported comparable morbidity and mortality rates for total pancreatectomy (47% and 5%, respectively) and pancreatoduodenectomy (32% and 3%, respectively) [1]. Studies estimate that a period of 10–20 years is required from the time of an initiating mutation to the establishment of advanced disease, suggesting a prolonged period during which intervention may be possible [4]. By identifying and screening patients at increased risk of developing PC, detection of precursor and early-stage lesions may allow diagnosis at a surgically resectable stage [3].

Risk factor reduction is advocated as the best preventive strategy [1]. Smoking significantly increases the risk of PC in the setting of HP [1, 17]. Members of HP kindreds should be counseled to avoid smoking and should exhibit the HP phenotype and/or genotype [1]. Physicians should strongly encourage smoking cessation in current smokers [1].

Another possible preventive measure is the risk factor reduction for decrease in the frequency of episodes of acute pancreatitis that might delay progression to chronic pancreatitis [1]. Elimination of known factors to cause chronic pancreatitis independently of HP may also help to slow disease progression [1].

Based upon this theory, it is recommended that those exhibiting the HP phenotype and/or genotype refrain from alcohol use [1]. Medications known to cause pancreatitis should be avoided when possible [1]. Metabolic derangements including hypertriglyceridemia and hypercalcemia should be corrected [1]. Patients exhibiting the HP phenotype should undergo radiologic and endoscopic evaluation in an attempt to identify and treat structural problems (e.g., choledocholithiasis, dominant pancreatic duct stricture) which may contribute to recurrent attacks of acute pancreatitis and/or progression to/of chronic pancreatitis [1].

Patients meeting the FPC definition or those with known inherited cancer syndromes with a family history PC may consider a PC surveillance program [5]. Thus, it is generally recommended that surveillance of these patients only be performed in centers experienced in caring for these high-risk patients, ideally enrolling them into research protocols [5]. At-risk relatives who meet the FPC criteria warrant pancreatic surveillance; however, the type, frequency, and age to begin surveillance are not yet well defined [18]. Some centers utilize EUS and/or MRI surveillance programs, both of which detect pancreatic lesions better than CT [18]. However, only precancerous or early-stage (I–II) PC is surgically resectable [3]. Since 5-year survival rate for patients diagnosed with Stage IA disease is 19 times that of those diagnosed with Stage IV disease (13.6% vs. 0.7%), greater improvements in survival may be seen if we focus on shifting the diagnosis of PC from a late stage to an early or precancerous stage [3]. Unfortunately, early-stage PC is often clinically silent, highlighting the need for improved methods of early detection of precursor and early-stage lesions [3].

World Health Organization guidelines suggest that in order to screen for a cancer, there must be a recognizable latent or early stage of the disease that can be tested for and managed effectively [3]. Several pancreatic lesions meet the criteria for a precursor to PC: pancreatic intraepithelial neoplasias (PanINs), mucinous cystic neoplasms (MCNs), and intraductal mucinous cystic neoplasms

(IPMNs) [3]. The incidence of IPMN has increased in the absence of a rise in IPMN related to overall PC-related mortality, so it likely results from an increase in diagnostic scrutiny, rather than greater numbers of patients with clinically relevant disease [19].

Due to high cost, relative inability of noninvasive imaging modalities to detect small, solid tumors, and the modest risks associated with screening techniques like EUS, the use of biomarkers for the early detection of PC is an important frontier [3]. Carbohydrate antigen 19-9 (CA 19-9) is the only FDA-approved blood biomarker test for PC; however, due to the low prevalence of PC in the population, CA 19-9 is recognized as a poor screening tool: a screening of over 10,000 patients found only four cases of PC based on CA 19-9 levels with three of those cases being not resectable at diagnosis [3, 14]. The sensitivity (70%), specificity (87%), positive predictive value (59%), and negative predictive value (92%) are still not high enough to be used regularly in healthy patients [14]. CA 19-9 levels do appear to be informative as a predictor of disease recurrence post-resection [14]. There is an ongoing research that suggests a future for gene expression profiling, proteomics, metabolomics, and microRNA as diagnostic PC biomarkers [14].

The low absolute risk of developing PC precludes population-wide screening at the current time, both from a cost-benefit and absolute harm perspective. Assuming a lifetime risk of developing PDAC of 1.49%, a hypothetical screening test with 90% sensitivity and specificity would have a positive predictive value (PPV) of just 12%, meaning that almost nine in ten positive screening results would be incorrect, with those patients subject to unnecessary stress and further testing [3]. Even a screening test with 95% sensitivity and specificity would result in a PPV of just 22% [3]. Notwithstanding, the identification of genetic and environmental risk factors may provide opportunities to enrich the screening population with high-risk cohorts, which would drastically increase the PPV of screening results, with the hopes of identifying precursor or early-stage

lesions in some high-risk individuals before the lesions progress to inoperable PC [3].

Timing of screening is controversial. CAPS recommends for Peutz-Jeghers patients to have EUS with or without MRI/MRCP starting at age 50, while expert opinions recommend EUS and CA 19-9 every 2 years starting at age 25 with or without CT scan [2, 10]. When a solid lesion is detected, CT scan should also be performed (grade low) [2].

No consensus was reached on the role of EUS-guided fine needle aspiration (FNA) to evaluate solid or cystic lesions in asymptomatic HRIs [2]. The role of EUS-FNA in the clinical management of most pancreatic cysts is limited, given the low accuracy of cytology in cystic lesions and the low volume of cyst fluid aspirated from small cysts [2]. False-positive cytology from subcentimeter solid indeterminate lesions may also lead to unnecessary surgery [2]. The general agreement is that patients should be fully counseled regarding the potential risk/benefits ratio of available screening modalities before enrollment in any protocol [1].

Physicians caring for a patient with HP in these circumstances should contact a pancreatologist expert in the care of HP for advice concerning the best imaging modality based on local equipment and expertise [1]. Optimally, screening should be performed within multicenter institutional review board-approved protocols that also include standardized collection and storage of blood/serum and pancreatic juice [1]. While many investigators advocate yearly screening, the frequency of screening may vary within particular prospective studies [1].

Outcome

The patient continues with standard screening for PJS patients including annual physical examination with complete blood count to detect iron deficiency anemia, colonoscopy, EGD, video capsule endoscopy every 3 years, and annual testicular exams. He will continue with MRCP or EUS every 1–2 years surveillance which would ideally have been initiated at age 25 for PC screening. Screening should

only be performed at centers of expertise in the setting of a research protocol. He also will undergo genetic counseling.

Clinical Pearls/Pitfalls

- PC is the fourth most common cause of cancer-related deaths in the USA.
- With low 5-year survival rates, significant advances in the understanding of PC etiology and tumor biology, early detection, screening, and treatment are necessary.
- Given that only early or precancerous stages have reasonable expectation of low morbidity and mortality, increased efforts are imperative to improve risk stratification and early identification, while PC is still resectable in early-stage disease or premalignant conditions.
- PC screening efforts may allow identification of effective modalities for screening and early detection.
- Screening for hereditary pancreatic cancer is based on consensus opinion and only guideline based.
- Although there is little data, it is encouraging and suggestive of decreasing mortality.
- Screening should be conducted in a registry or trial with a referral to a center of excellence.
- Reduce risk attributed to modifiable risk factors: tobacco exposure, alcohol use, chronic pancreatitis, diet, obesity, diabetes mellitus, and certain abdominal surgeries and infections.

References

1. Ulrich CD. Consensus Committees of the European Registry of Hereditary Pancreatic Diseases MM-CPSG, International Association of Pancreatology. Pancreatic cancer in hereditary pancreatitis: consensus guidelines for prevention, screening and treatment. Pancreatology. 2001;1(5):416–22.
2. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the

management of patients with increased risk for familial pancreatic cancer. Gut. 2013;62(3):339–47.
3. Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. World J Gastroenterol. 2014;20(32):11182–98.
4. Humphris JL, Johns AL, Simpson SH, et al. Clinical and pathologic features of familial pancreatic cancer. Cancer. 2014;120(23):3669–75.
5. Solomon S, Das S, Brand R, Whitcomb DC. Inherited pancreatic cancer syndromes. Cancer J. 2012;18(6):485–91.
6. Grover S, Syngal S. Hereditary pancreatic cancer. Gastroenterology. 2010;139(4):1076–80, 1080.e1071–72.
7. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. J Natl Cancer Inst. 2010;102(2):119–26.
8. Rebours V, Lévy P, Ruszniewski P. An overview of hereditary pancreatitis. Dig Liver Dis. 2012;44(1):8–15.
9. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53.
10. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105(6):1258–64; author reply 1265.
11. McGarrity T, Amos C. Peutz-Jeghers syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington; 1993–2016. 2001 Feb 23 [Updated 2016 Jul 14].
12. Lim W, Hearle N, Shah B, et al. Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome. Br J Cancer. 2003;89(2):308–13.
13. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2(1):41–6.
14. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002;94(18):1365–72.
15. Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 2011;71(6):2222–9.

16. DiMagno EP, Reber HA, Tempero MA. AGA technical review on the epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. American Gastroenterological Association. Gastroenterology. 1999;117(6):1464–84.
17. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89(6):442–6.
18. Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142(4):796–804; quiz e714–95.
19. Klibansky DA, Reid-Lombardo KM, Gordon SR, Gardner TB. The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol. 2012;10(5):555–8.

Chapter 12
Optimizing Nutrition for the Patient after Pancreaticoduodenectomy: Pancreatic Insufficiency

Jeannine B. Mills

Case Study

A 52-year-old with history of pancreatic cancer who was well nourished preoperatively underwent Whipple resection and gastrojejunostomy. The patient reports to surgery clinic 4 weeks postoperatively and has a weight of 129 lbs, decreased appetite, dysgeusia, early satiety, and intolerance to higher fat foods; he has an obvious loss in lean body mass based on nutrition focused physical assessment. He describes his bowel movements as yellow, oily, and malodorous.

My Management

A. Start on pancreatic enzyme replacement therapy after diagnosis of exocrine pancreatic insufficiency (EPI).

J.B. Mills, MS, RDN, CSO, LD
Gastrointestinal Cancer Group, One Medical Center Drive, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, USA
e-mail: Jeannine.B.Mills@Hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_12,

May not be necessary to dose via J-tube with semi-elemental or elemental enteral formulas vs. isotonic enteral formulas.

B. There is a risk of clogging jejunostomy tube and/or decreasing efficacy of enzymes, but pancreatic enzyme capsules can be opened and emptied into either thickened acidic liquid suspension or thin food (apple sauce) or mixed with sodium bicarbonate to then infuse via J-tube.
C. Dosing recommendations are 1000–2000 IU/kg lipase per meal or 25,000–50,000 IU lipase for main meal and 10,000–25,000 IU lipase for snacks, without exceeding 10,000 IU/kg lipase per day. Lipase per meal titrates up as the volume of food increases and/or signs/symptoms of EPI are apparent.
D. Dose enzymes with first bite of food and throughout meal. This may make a difference for some patients though may also be dependent on transit time of food through the gut postoperatively.

Diagnosis and Assessment

Malnutrition is prevalent in pancreatic cancer and may have significant and adverse impact on quality of life and overall survival. It is estimated that more than 80% of patients with pancreatic adenocarcinoma will have weight loss at the time of presentation. Malnutrition "should be considered a significant independent risk factor in patients with pancreatic cancer and one of the primary goals of treatment should be to improve nutritional status." Studies demonstrate that improvement in nutrition status is correlated with better survival and quality of life despite stage of disease [1–6].

Patients with pancreatic cancer also experience the highest incidence of cachexia estimated at 70–80% and is associated with poorer disease and surgical outcomes. The impact of cachexia on prognosis and outcome is significant including reduced treatment tolerance, worsened postoperative outcome, higher rates of metastatic disease, more progressive

disease, reduced survival, and of course decreased quality of life. Malabsorption through EPI is an exacerbating factor of cachexia in pancreatic cancer [2].

Weight loss in pancreatic cancer is associated with reduced survival. It was found that a weight loss of >5% and ≤10% of total body weight provided a 3.9-fold higher relative risk of death than those without weight loss, while a weight loss >10% of total body weight provided a sevenfold higher relative risk of death than those without weight loss [7].

In surgical patients, malnutrition and cachexia have been associated with infection, poor wound healing, increased postoperative complications, increased length of stay, and increased morbidity [8, 9]. Postoperative weight loss is an independent prognostic factor. Hashimoto et al. showed that severe weight loss is associated with poor prognosis and a trend toward shorter survival [10].

Exocrine pancreatic insufficiency in pancreatic cancer is very common with 25–45% having preoperative EPI and 50–80% of patients continuing to experience EPI post surgery at 3 months, 1 year, and 2 year postoperatively. One study reported steatorrhea worsening postoperatively, with return to baseline by 12 months [11–13].

Management

The deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition. Exocrine enzyme insufficiency is common and progressive. Patients should be regularly screened for symptoms of enzyme insufficiency. Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency [14, 15].

Because pancreatic exocrine insufficiency occurs in up to 94% of patients undergoing pancreatic surgery and 50–89% of nonsurgical patients, therapy may be initiated based on

symptomatology without diagnostic tests. Pancreatic enzyme replacement therapy helps maintain weight and quality of life in patients with unresectable pancreatic cancer [5, 14].

Outcome

Postoperatively, once EPI is identified and managed with pancreatic enzymes, the patient was able to eat more comfortably with improved digestion and begins to maintain or even gain weight and experience improvement in quality of life.

Clinical Pearls/Pitfalls

- Symptoms of EPI are often nonspecific, so a high index of clinical suspicion is needed to make a correct diagnosis, important to assess in virtually all pancreatic cancer patients.
- Patients and caregivers should be instructed on recognizing signs and symptoms of EPI, and it is not uncommon to ask patients to keep a diary.
- Patients should be reminded on taking their enzymes at first bite of eating, and sometimes there is improvement if dosed throughout the meal.
- Too often patients under dose enzymes per meals do not find improvement in symptoms so they will discontinue completely.
- Patients with a clinical suspicion of pancreatic exocrine insufficiency despite appropriate replacement should receive a more thorough nutritional evaluation by a registered dietitian nutritionist.
- Some private insurers as well as Medicare and Medicaid may not provide coverage of enzyme replacement. Some pharmaceutical companies may offer patient vouchers for assistance or online patient assistant programs.

- Excellent patient resources regarding EPI and pancreatic enzymes are available to patients and caregivers on websites such as Pancreatic Cancer Action Network (www.pancan.org) as well as National Pancreas Foundation (www.npf.org).

References

1. Bauer JD, Capra S. Nutrition intervention improves outcomes in patients with cancer cachexia receiving chemotherapy—a pilot study. Support Care Cancer. 2005;13(4):270–4.
2. Mueller TC, Burmeister MA, Bachmann J, Martignoni ME. Cachexia and pancreatic cancer: are there treatment options? World J Gastroenterol. 2014;20(28):9361–73.
3. Vashi P, Popiel B, Lammersfeld C, Gupta D. Outcomes of systematic nutritional assessment and medical nutrition therapy in pancreatic cancer. Pancreas. 2015;44(5):750–5.
4. Davidson W, Ash S, Capra S, Bauer J, Cancer Cachexia Study Group. Weight stabilization is associated with improved survival duration and quality of life in unresectable pancreatic cancer. Clin Nutr. 2004;23(2):239–47.
5. Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. Gut. 2005;54(Suppl 5):v1–16.
6. Victorian Department of Health and Human Services. Optimal care pathway for people with pancreatic cancer. http://www.cancervic.org.au/downloads/health-professionals/optimal-carepathways/Optimal_care_pathway_for_people_with_pancreatic_cancer.pdf. Accessed Nov 2016.
7. Papadoniou N, Kosmas C, Gennatas K, Polyzos A, Mouratidou D, Skopelitis E, Tzivaras M, Sougioultzis S, Papastratis G, Karatzas G, Papalambros E, Tsavaris N. Prognostic factors in patients with locally advanced (unresectable) or metastatic pancreatic adenocarcinoma: a restrospective analysis. Anticancer Res. 2008;28(1B):543–9.

8. Kanda M, Fujji T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg. 2011;98(2):268–74.
9. LaTorre M, Ziparo V, Nigri G, Cavallini M, Balducci G, Ramacciato G. Malnutrition and pancreatic surgery: prevalence and outcomes. J Surg Oncol. 2013;107(7):702–8.
10. Hashimoto D, Chikamoto A, Ohmuraya M, et al. Impact of postoperative weight loss on survival after resection of pancreatic cancer. JPEN. 2015;39(5):598–603.
11. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. Br J Surg. 2014;101(2):109–13.
12. Matsumoto J, Traverso W. Exocrine function following the whipple operation as assessed by stool elastase. J Gastrointest Surg. 2006;10(9):1225–9.
13. Park JW, Jang JY, Kim EJ, Kang MJ, Kwon W, Chang YR, Han IW, Kim SW. Effect of pancreatectomy on nutritional state, pancreatic function and quality of life. Br J Surg. 2013;100(8):1064–70.
14. Bartel MJ, Asbun H, Stauffer J, Raimondo M. Pancreatic exocrine insufficiency in pancreatic cancer: a review of the literature. Dig Liver Dis. 2015;47(12):1013–20.
15. Tseng DS, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. Pancreas. 2016;45(3):325–30.

Chapter 13
Palliative Care and Pancreatic Disease

Amelia M. Cullinan

Case Study

Fred is a 57-year-old man who was referred to medical oncology for consultation regarding metastatic adenocarcinoma of the head of the pancreas. Previously healthy, his presenting symptom had been painless jaundice, s/p ERCP and biliary stenting. CT imaging completed 1 week ago demonstrates a lesion in the head of the pancreas, encasing the SMA, and several metastases in the R lobe of the liver. His chemistries and liver function tests are within normal limits, and CA19-9 is 650 U/mL. At the visit, he complains of a 2-week history of increasing deep epigastric pain, which increases with movement of the torso, as a result of which he has been limited to spending his days in bed or a chair. He is a construction foreman and last worked 3 weeks ago. One week ago, his primary care physician prescribed acetaminophen 325 mg/hydrocodone 10 mg tablets, which has

A.M. Cullinan, MD
Assistant Professor of Medicine, Geisel School of Medicine, Director, Outpatient Palliative Care Services, Section of Palliative Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: amelia.m.cullinan@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_13,

been taking consistently every 4 h around the clock. This dose reduces his pain from a nine out of ten on a visual analog scale to 7/10. Doubling the dose causes unacceptable sedation. He has a history of severe delirium with morphine. He has not moved his bowels in 4 days and is not taking a bowel regimen. He states he has no interest in eating and feels mildly nauseous at times, with early satiety and post-prandial bloating. He denies steatorrhea. He has lost 10 pounds in the last month. On exam, he is seated in a wheelchair, well built with no evidence of muscle wasting, withdrawn but willing to engage if directly addressed. He shifts position frequently. His abdomen is distended, with quiet bowel sounds and epigastric tenderness to deep palpation. On a review of social history, he and his wife Sally are guardians for their 17-year-old grandson Matt; their daughter struggles with substance abuse. Sally has multiple sclerosis and needs help with shopping and cleaning their home; since Fred has been ill, they have depended on Matt for these tasks, but worry about the effect on his schoolwork. It is important to Fred that he live long enough to see Matt graduate from high school in 4 months, and he is motivated to try chemotherapy or clinical trials. In addition, Fred mentions that he is fearful about taking high-dose opioids given the family history of addiction and asks about non-opioid strategies to manage his pain.

The oncologist explains to Fred and Sally that unfortunately, with his poor functional status (ECOG 3), he is likely to experience worsened quality of life and decreased length of life on chemotherapy. He is referred to hospice.

My Management

A. Refer to palliative care.
B. Symptom management, follow-up in 4 weeks.
C. Discuss the option of chemotherapy if functional status improves.

Diagnosis and Assessment

Delivering Bad News and Elicitation of Goals

For many clinicians, delivering the bad news of a terminal illness is stress-inducing: they worry that the patient might experience a strong emotional response, and so they seek to soften the news as much as possible. The unintended consequence of this is that the patient may not hear all of the information they need to and then make uninformed healthcare decisions: for example, a patient might understand that they have longer to live than is likely and choose to pursue a more aggressive treatment regimen which takes them away from doing the things they love [1].

The essential steps in delivering the news of a terminal diagnosis are (1) assess the patient's understanding of their illness and information preferences; (2) provide a prognosis, framed in a patient-centered way; and (3) respond empathically to emotion [1]. Sample language for this process is given in Table 13.1. Approximately 20% of patients will not be ready to hear any prognostic information at all: the clinician should explore the patient's reasons for not learning this information and tailor their response accordingly [2].

After allowing the patient time to process this information, the clinician should explore the patient's values and goals. With that information, the clinician can offer a tailored treatment recommendation—whether supportive care or cancer-directed therapy—specific to the patient. The Serious Illness Communication Guide is a structured communication tool developed for use in oncology patients whom their clinician suspects to have a prognosis of less than a year (Fig. 13.1); it guides clinicians through the steps of goals of care conversation.

In addition to providing information in a hopeful, patient-centered way, the clinician can provide hope by demonstrating mastery of symptom management; for many cancer patients, fear of uncontrolled symptoms can influence them

Table 13.1 Relaying prognostic information

Step	Sample language
Assess illness understanding (prognostic awareness)	"What have you learned so far about your cancer diagnosis?"
Assess information preferences	"I'd like to assure that I am giving you the information you need. When you ask how long do you have, I wonder if you are looking for average life expectancy or whether you will make it to an important life event?"
Deliver prognostic information, tailored to patient:	
Timing	"If 100 patients like you chose not to receive chemotherapy, at most 50 of them would still be alive at 6 months. If 100 patients like you received this chemotherapy regimen, I expect that 35 would still be alive at 1 year."
Specific event	"I think it is likely that you will make it to your daughter's wedding in 4 months."
Respond empathically to emotion (NURSE)	
Naming	"I can see how sad this makes you."
Understanding	"Of course this is devastating news."
Respecting	"You are so resilient in the face of this tough news."
Supporting	"I'm going to be with you through all of this."
Exploring	"Can you give me a sense of what you're thinking?"

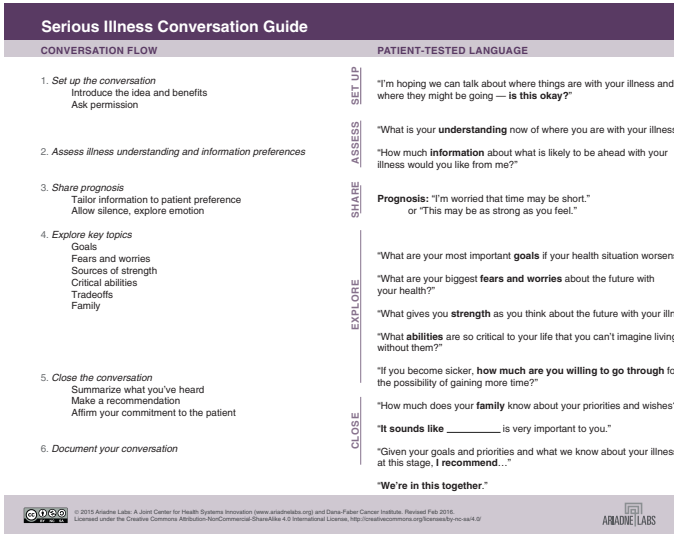

FIGURE. 13 1 Serious Illness Conversation Guide. Reprinted with permission from 2015 Ariadne Labs: A Joint Center for Health Systems Innovation (www.ariadnelabs.org) and Dana-Farber Cancer Institute

to make decisions which are not otherwise in line with their stated goals [1]. Three common symptoms in pancreatic cancer are pain, weight loss, and mood disorders. The clinician should perform a careful symptom assessment at each visit.

Assessment: Pain

A careful pain assessment allows the clinician to accurately identify the generators of each pain syndrome and target their therapy correctly [3]. A helpful mnemonic to use is PQRST, shown in Table 13.2.

The most common pain syndromes in pancreatic cancer will be reviewed here, organized by location of disease. Tumors located in the head of the pancreas can cause

Table 13.2 Elements of pain assessment

P	Precipitators and palliators (relievers: pharmacologic and non-pharmacologic)
Q	Quality • Visceral (poorly localized, deep, dull, difficult to characterize) • Neuropathic (following dermatomes or characteristic stocking-glove distribution; tingling/burning/allodynia/hypoesthesia) • Somatic (localized, sharp, reproducible)
R	Region (focal, diffuse), Radiating
S	Severity (numerical rating scale, 0–10; categorical rating scale, mild/moderate/severe; Faces Pain Rating Scale)
T	Timing (intermittent, variable, or stable/constant)

a visceral epigastric pain syndrome, often described as boring through to the back; sensory innervation from the entire upper abdomen is transmitted through the celiac plexus. When tumor invades the celiac plexus itself, a neuropathic pain syndrome, classically belt-like, radiating from the epigastrium around to the mid-back or vice versa, is common. Liver metastases, when peripheral and either stretching or involving the highly innervated liver capsule, cause an inflammatory visceral pain syndrome; subdiaphragmatic lesions can result in referred pain to the R shoulder. Bulky retroperitoneal lymphadenopathy can cause a visceral back pain syndrome which is classically relieved by hunching forwards; the position shifts the retroperitoneal capsule, which is highly innervated, off of the lymph nodes. Peritoneal carcinomatosis can cause either an inflammatory, diffuse peritoneal pain when nodules invade the peritoneum, or a visceral, cramping pain due to partial small bowel obstruction by tumor deposits. Finally, invasion of the duodenum or gastric wall by tumor can cause an epigastric nociceptive pain syndrome, exacerbated by eating, as gastric juices flood the ulcerated area.

Assessment: Weight Loss

Weight loss in pancreatic cancer can be due to one or more syndromes which often overlap. Syndromes which impact caloric intake or absorption of nutrients can often be reversed or significantly improved with good symptom management.

Pancreatic insufficiency is common with tumors located in the head of the pancreas and presents with abdominal cramping, flatulence, urgency to defecate, and weight loss. Steatorrhea, the most singular symptom of this constellation, does not develop until lipase concentrations fall below 10% of normal, so a high clinical suspicion for this syndrome is warranted [4].

Early satiety can be due to benign causes of gastroparesis (autonomic dysfunction, medications, prior gastrointestinal surgery, or celiac plexus neurolysis) or malignant gastroparesis: in one study, 60% of patients with pancreatic cancer and without gastroduodenal invasion or obstruction experienced abnormally delayed gastric emptying [5]. In the absence of obstruction, which is ruled out by upper gastrointestinal endoscopy or radiographic series, the pathophysiology of gastroparesis in pancreatic cancer patients is due to disruption of the vagus nerve or enteric neural tissues by micrometastases, paraneoplastic antineuronal antibodies, or production of inhibitory neurotransmitters by the tumor [6]. Nonobstructing malignant gastroparesis is diagnosed by gastric emptying scintigraphy.

Anorexia can be the result of severe fatigue, poorly controlled nausea, pain, or depression, xerostomia, stomatitis, or dysgeusia.

In contrast to the weight loss syndromes above, cancer-related anorexia-cachexia syndrome (CACS) cannot be reversed when intake or absorption is improved. The European Palliative Care Research Collaborative defines CACS as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [7]. The pathophysiology is characterized by a negative protein and

energy balance driven by a variable combination of reduced food intake and abnormal metabolism (EPCRC). Its prevalence in advanced, unresectable pancreatic cancer patients is 60–80%, and in one study, it was associated with a median survival of 21 weeks [8]. Fearon et al. have proposed a three-factor classification to diagnose cachexia, requiring the presence of at least two of three factors: weight loss >10%, low food intake (≤1500 kcal/day), and systemic inflammation (CRP > 10 mg/mL) [9].

Assessment: Mood

Patients with pancreatic cancer are more likely to experience mood disorders (anxiety, depression, or a mixed state) than patients with other cancer diagnoses: Prevalence rates for combined mood disorders in recent studies ranged from 36 to 57% [10, 11], and undertreatment of these conditions impacts patients' quality of life. In addition to the mood-specific symptoms of anxiety or depression, an untreated mood disorder can masquerade as, or intensify the experience of, other cancer-related symptoms, such as pain, dyspnea, nausea, and anorexia, and can lead to reductions in performance status, thereby potentially interfering with patients' ability to tolerate chemotherapy.

Screening for depression in the cancer population is challenging because many of the physical symptoms of depression (fatigue, weight loss, insomnia or hypersomnia, and poor concentration) can result from the cancer process itself. Therefore, experts recommend the use of psychological symptoms instead [12]. It is also important to distinguish depression from preparatory grief, which is a normal part of incurable cancer patients' preparation for death, and features rumination about the past, intermittent withdrawal from family/friends, and times of sadness, crying, or anxiety [13]. Table 13.3 compares these diagnostic criteria to one another. Consider the diagnosis of adjustment disorder when a patient has depressed symptoms but none of the above criteria are

Table 13.3 Diagnosing depression and anticipatory grief in cancer

Depression (DSM-5)	Depression in cancer (Endicott)	Preparatory grief (Periyakoil)
Depressed mood most of the day, nearly every day	Depressed mood most of the day, nearly every day	Depressed mood only some days
Anhedonia: markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day	Anhedonia: markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day	Not present
Significant weight loss or weight gain or decrease or increase in appetite nearly every day	Depressed appearance, tearfulness	Not present
Insomnia or hypersomnia nearly every day	Social withdrawal or decreased talkativeness, refractory to social support	Social withdrawal is common but improves with social support
Psychomotor agitation or retardation nearly every day	Psychomotor agitation or retardation nearly every day	Not present
Fatigue or loss of energy every day	Brooding, self-pity, or pessimism	Rumination, often about the past. No self-pity or pessimism
Feelings of worthlessness or excessive or inappropriate guilt nearly every day	Feelings of worthlessness or excessive or inappropriate guilt nearly every day	Guilt, often about missing future family events. No worthlessness

(continued)

Table 13.3 (continued)

Depression (DSM-5)	Depression in cancer (Endicott)	Preparatory grief (Periyakoil)
Diminished ability to think or concentrate, or indecisiveness, nearly every day	Lack of reactivity, blunting	Not present
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide	Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide	Not present

Adapted from American Psychiatric Association; Endicott; Periyakoil

met [14]. Finally, some statements of apparent suicidality (e.g., "I wish I were dead") can be clues to poorly controlled symptoms (i.e., pain) and should be explored before assuming they relate to depression.

Symptoms of anxiety can be related to medical illness; the clinician should be mindful of possible medication side effects (corticosteroids, some antidepressants, psychostimulants) or withdrawal symptoms (alcohol, opioids, benzodiazepines, clonidine, antidepressants, gabapentin, and corticosteroids), as well as undertreated symptoms (dyspnea, pain), and treat these appropriately. When anxiety is a predominant and limiting symptom and the previous etiologies are not present, the clinician should take a psychiatric history, inquiring about prior episodes of anxiety or depression, PTSD, alcohol, or drug use, prior or current treatment with a mental health professional, or past psychiatric hospitalizations. In addition, the clinician should assess for the presence of panic attacks (pounding heart, sweating, trembling, shortness of breath or choking, dizzy/lightheaded, fear

of losing control, or derealization), or lifelong phobias. Patients who screen positive for any of the above elements should be referred to a psychiatry or palliative care practitioner.

Management

The primary tools used to palliate the symptoms of advanced pancreatic cancer are symptom-based medications and procedures, which will be described below. Palliative chemotherapy is appropriate for patients with adequate functional status (ECOG ≥ 2), and even in the absence of objective response, single agent gemcitabine improved clinical benefit response (pain, weight loss, and functional status) [15]. Finally, early integration of palliative care consultants, when available, improves clinical and quality of life outcomes and may improve survival [16]. As a result, early referral to palliative care is now part of ASCO clinical practice guidelines for advanced pancreatic cancer [17].

Management: Pain

In advanced pancreatic cancer, as in other malignancies, analgesic therapy should be targeted to the presumed etiology of pain. The patient's response to therapy should be monitored frequently, and analgesic doses should be titrated rapidly to achieve improved functioning and reduced pain scores while avoiding excessive sedation, constipation, and other side effects. Adjuvant agents can be used either to forestall the need for opioids or to reduce overall opioid requirements, and in some cases, can reduce non-pain symptom burden as well.

Acetaminophen is appropriate as a single agent for mild pain (NRS scores of 1–3 out of 10) and can potentiate the effect of other analgesics. In patients without cirrhosis, the total dose should be kept under 4 g/day when used short term and under 3 g/day for long-term use.

NSAIDs and corticosteroids are useful for visceral inflammatory pain syndromes, such as hepatic capsule stretch due to bulky metastases; somatic inflammatory pain syndromes, such as peritoneal metastases/carcinomatosis; and somatic bony pain due to metastases. Both are effective, but the side effect profiles of each usually dictate the choice of therapy. NSAIDs should be avoided in patients on anticoagulation, those receiving chemotherapy which causes thrombocytopenia, or patients with chronic kidney disease or gastric/duodenal ulcer disease, but for patients without these concerns, NSAIDs can be used long term, unlike corticosteroids. Consider starting with naproxen 220 mg BID or ibuprofen 600 TID. When used over weeks to months, corticosteroids carry significant risks of proximal muscle weakness, immunosuppression, impaired wound healing, and osteoporosis, so they are ideally used as a bridge to other therapy. Among corticosteroids, dexamethasone is most commonly used because it is least likely to cause fluid retention, is potent, and has a long half-life, allowing once-daily administration. The most appropriate dose for relief of cancer-related pain has not been studied, but in general use, doses in the range of 2–8 mg qAM are common [18].

For neuropathic pain, such as the stocking-glove dysesthesias associated with chemotherapy-induced neuropathy, or the band-like abdominal neuropathic pain caused by celiac plexus invasion by tumor, anticonvulsants, such as gabapentin or pregabalin, should be offered first. In patients with normal renal function, gabapentin can be initiated at 300 mg/day and immediately titrated every 3 days to 900 mg/day in three divided doses, with a maximum dose of 3600 mg/day. Adjusted dosing and/or slower titration are recommended in the elderly or those with renal impairment. The SNRI antidepressants (duloxetine and venlafaxine) are approved for diabetic neuropathy and could be considered when a patient presents with both depression and neuropathic pain. Topical anesthetics, such as lidocaine, require application multiple times a day and are most feasible for focal, localized pain syndromes, such as dermatomal pain from a zoster infection or spine metastasis.

Weak opioids, such as codeine and tramadol, should be offered to patients with mild (NRS 1–3 out of 10) pain who have not benefited from adjuvant agents or over-the-counter medication, or who cannot yet tolerate stronger opioids.

Strong opioids, such as morphine, oxycodone, hydromorphone, and fentanyl, are recommended for moderate to severe cancer pain (4–10 on NRS). Bandieri et al. found that weak opioids were not as effective as strong opioids in managing moderate cancer pain and were similarly tolerated [19]. When initiating therapy with strong opioids, short-acting agents should be used first, and the dose is titrated to achieve adequate analgesia. When pain is persistent and requires regular use of short-acting agents, clinicians should consider adding a long-acting release agent (e.g., sustained-release morphine or transdermal fentanyl), dosed at 50% of the equianalgesic total short-acting daily dose [3].

Methadone is a synthetic opioid whose unique properties include NMDA receptor antagonism. The NMDA receptor, in the central nervous system, is implicated in the development of opioid tolerance and hyperalgesia; as a result, methadone is commonly used when patients with moderate to severe nociceptive or neuropathic pain have become refractory or tolerant to traditional opioids. It is also a good choice for patients with renal failure as it is cleared hepatically. There is no evidence to support its use as a first-line agent: in a randomized double blind study comparing methadone to morphine for first-line use in cancer pain, Bruera et al. found equal efficacy in relief of neuropathic pain, suggesting that it should remain a second- or third-line agent [20]. Additionally, methadone has highly variable pharmacokinetics across patients and interacts with a large number of commonly used medications in oncology, leading to risk of accumulation and opioid overdose, so guidelines recommend consultation with a pain or palliative care clinician before prescribing methadone [3].

To prevent opioid-induced constipation when initiating opioids for cancer pain, guidelines recommend prophylactic use of a laxative bowel regimen (Senokot two tablets

daily or polyethylene glycol 17 g in 8 ounces of water twice daily) and titration according to response and with titration of opioids; constipation is a dose-related side effect of opioid therapy.

For epigastric and upper abdominal pain in pancreatic cancer, celiac plexus neurolysis can reduce opioid requirements durably, reducing the associated adverse effects of opioid therapy [21]. The celiac plexus, a dense knot of autonomic nerves just posterior to the pancreas, receives afferent nociceptive signals from the upper abdominal viscera (pancreas, distal third of the esophagus to the transverse colon, liver and biliary tract, the adrenals, and mesentery), and therefore alcohol lysis of the plexus can effectively "block" pain signals from traveling to the central nervous system. The best evidence for this procedure is in patients with pancreatic cancer with predominantly visceral pain, as the celiac plexus does not transmit somatic pain signals (e.g., inflammatory pain from peritoneal involvement) [21]. Within that population, celiac plexus neurolysis should be considered for patients who are experiencing adverse effects from opioids which are refractory to opioid rotation. The procedure is generally well tolerated, carrying a risk of transient diarrhea and hypotension due to interruption of sympathetic blockade, generally lasting no longer than 2 weeks [21].

Management: Weight Loss

When addressing weight loss in advanced pancreatic cancer, clinicians should assess for and treat any reversible processes, as described above. Problems with caloric intake or absorption are often amenable to appropriate therapy. Pancreatic insufficiency is common and the management of this complication is described in Chap. 12.

Early satiety and nausea should be addressed by targeting the underlying etiology: in cases of malignant ascites, regular paracentesis or placement of an indwelling peritoneal catheter

can improve early satiety and aggressively treat constipation. Chemotherapy-induced nausea should be aggressively managed according to NCCN Guidelines [22]. Though prokinetics (metoclopramide, domperidone, tegaserod, cisapride) have been shown to increase weight in patients with nonmalignant gastroparesis, in a study of patients with malignant gastroparesis, metoclopramide improved nausea, vomiting, and bloating, but did not improve appetite; its impact on weight was not measured [23].

When poor appetite appears related to an uncontrolled mood disorder, mirtazapine may improve weight and appetite [24]. Another potential contributor to anorexia can be xerostomia, a side effect common for antiemetics, opioids, and antidepressants used to manage other symptoms in advanced pancreatic cancer. Where possible, eliminate or reduce offending agents; when this is not possible, cholinergic agonists such as pilocarpine and cevimeline can be used.

Anorexia-cachexia syndrome, common in advanced pancreatic cancer, is thus far refractory to most therapies. In numerous studies, a wide variety of agents, including appetite stimulants, anabolic agents, cytokine and metabolic inhibitors, and others, have failed to reverse cachexia and demonstrated lack of superiority to corticosteroids and progesterone analogs, though even these agents do not reverse cachexia. Both corticosteroids and progesterone analogs (megestrol acetate) improve anorexia and weight loss, though the gains are in adipose tissue, not lean body mass. In a randomized controlled trial comparing Megace (800 mg daily), dexamethasone (0.75 mg QID), and the anabolic corticosteroid fluoxymesterone, dexamethasone and Megace were superior to fluoxymesterone and equivalent to one another in appetite stimulation and weight gain; notably, Megace carried a higher risk of deep venous thrombosis [25]. Given the increased risk of thromboembolism in pancreatic cancer, dexamethasone at a minimum dose of 4 mg/day is recommended for palliation of anorexia-cachexia syndrome [25].

Management: Mood

Advanced cancer patients with depression see sustained improvement in their symptoms from a multimodal strategy, incorporating pharmacologic, psychotherapeutic, and complementary strategies. Such care is optimally provided by outpatient palliative care or other supportive interdisciplinary teams [26, 27]. Patients with mild symptoms of depression or adjustment disorder can benefit from psychotherapy alone: the best evidence is for cognitive behavioral therapy, while support groups also appear effective [28]. Patients with moderate to severe depression will also require antidepressant therapy. Head-to-head data comparing the efficacy of different antidepressants is lacking, so clinicians are advised to select an antidepressant by targeting the drug's side effect profile to address the patient's predominant symptoms: more agitated, with symptoms of insomnia and rumination, or more withdrawn, with features of psychomotor retardation [29]. Clinicians should also take into account the patient's comorbid illnesses, risk factors for adverse effects, and other cancer-related symptoms. Table 13.4 outlines some of the most commonly used antidepressants and their side effect profiles.

Most patients with cancer experience symptoms of anxiety along the disease course; these symptoms are largely situational and self-limited. The minority of patients who experience limiting symptoms of anxiety will require intervention. For short-term symptoms of anxiety, benzodiazepines, such as lorazepam, are effective; longer-term use is not advised given the risk of increased fatigue, reduced concentration, tolerance, and addiction. As an alternative, buspirone is a nonaddictive anxiolytic. Cancer patients with long-term symptoms, or who endorse limiting symptoms of anxiety prior to their diagnosis, will benefit from antidepressant therapy with SSRIs or SNRIs. In addition to pharmacologic strategies, patients with moderate to severe symptoms of anxiety should be offered cognitive behavioral therapy to learn behavioral strategies to manage their symptoms [30].

Table 13.4 Selected antidepressants for advanced pancreatic cancer

Subtype	Class	Drug	Notes
Activating	SSRIs	Fluoxetine	Start low, titrate slowly to avoid GI toxicity
		Sertraline	
	Atypicals	Bupropion	Use with caution in patients with lowered seizure threshold; sustained-release preparations are lower risk
	Psychostimulants	Methylphenidate	Use as a bridge until SSRI takes effect in 2–4 weeks
		Modafinil	Can also be used to reduce sedation from opioids
Sedating	SSRIs	Paroxetine	Start low, titrate slowly to avoid GI toxicity
		Fluvoxamine	
	Atypicals	Mirtazapine	Stimulates appetite; antiemetic due to 5HT2 activity
	TCAs	Amitriptyline	Stimulate appetite; effective for neuropathic pain. Highly anticholinergic; avoid in patients with severe dry mouth or constipation. Avoid in patients at risk of arrhythmia
		Nortriptyline	
	Serotonin modulators	Trazodone	Useful at low dose for sleep disturbance

(continued)

Table 13.4 (continued)

Subtype	Class	Drug	Notes
Neutral	SSRIs	Citalopram	Start low, titrate slowly to avoid GI toxicity
		Escitalopram	
	SNRIs	Duloxetine	Also effective for neuropathy, fibromyalgia
		Venlafaxine	

Legend: *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *SNRI* serotonin-norepinephrine reuptake inhibitors

Outcome

After his oncology consultation, Fred's primary care physician starts him on transdermal fentanyl at a dose of 25 μg/h, with oxycodone 5–10 mg every 4 h as needed for breakthrough, as well as senna, two tabs twice daily, for constipation, which results in improvement in his pain, appetite, mood, and function. He declines hospice referral because he feels so well and instead seeks a second opinion at a regional cancer center. At that visit, his ECOG performance status has improved from 3 to 1, and he is offered gemcitabine plus nab-paclitaxel, as well as a palliative care consultation to assist with symptom management and psychosocial support and to help his wife Sally prepare for her care needs after his death. He enjoys good quality of life on chemotherapy, allowing him to continue supporting Sally for a number of months, and lives to attend his grandson's high school graduation. After 6 months on therapy, Fred's cancer progresses, and he elects to transition to hospice.

Clinical Pearls/Pitfalls

- Early outpatient integration of palliative care services, concurrent with anticancer therapies, can improve quality of life and clinical outcomes and may improve survival.
- With careful symptom management, cancer patients may regain adequate functional status to benefit from chemotherapy.
- Patients with moderate to severe (NRS score 4–10 out of 10) cancer pain should be treated with strong opioids (e.g., morphine, oxycodone, hydromorphone); weak opioids (e.g., codeine, tramadol) are not as effective and were similarly tolerated.
- Opioid rotation from one agent to another should be considered if pain does not respond to appropriate opioid dose titration, or if patients experience persistent limiting adverse effects.

- Celiac plexus neurolysis can durably reduce pain scores, opioid requirements, and opioid-related side effects in pancreatic cancer patients with visceral epigastric and upper abdominal pain.
- While cachexia is predictive of poor prognosis in pancreatic cancer, anorexia alone may be due to reversible processes such as constipation, poorly controlled pain, and nausea due to gastroparesis.
- When treating anorexia-cachexia syndrome, corticosteroids (e.g., dexamethasone) and progesterone analogs (e.g., Megace) are the most effective agents at improving anorexia and weight loss. There are no agents proven to reverse cachexia.
- Corticosteroids, rather than progesterone analogs, are the preferred short-term therapy for appetite stimulation in pancreatic cancer due to high risk of venous thromboembolism in this population.
- Untreated mood disorders can masquerade as, or intensify the experience of, cancer-related symptoms such as pain, dyspnea, nausea, and anorexia.
- When screening for depression in advanced cancer, somatic symptoms (fatigue, insomnia, anorexia) are poor predictors of depression; assess changes in affect (altered appearance, social engagement, ruminating thoughts) instead.
- When anorexia appears related to untreated depression, mirtazapine may improve appetite, nausea, and weight.

References

1. Campbell TC, Carey EC, Jackson VA, Saraiya B, Yang HB, Back AL, et al. Discussing prognosis: balancing hope and realism. Cancer J. 2010;16:461–6.
2. Back AL, Arnold RM. Discussing prognosis: "How much do you want to know?" Talking to patients who do not want information or who are ambivalent. J Clin Oncol. 2006;24(25):4214–7.

3. NCCN Clinical Practice Guidelines in Oncology Version 2.2016: Adult Cancer Pain. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 14 Oct 2016.
4. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol. 2011;26(Suppl. 2):12–6.
5. Barkin JS, Goldberg RI, Sfakianakis GN, Levi J. Pancreatic carcinoma is associated with delayed gastric emptying. Dig Dis Sci. 1986;31(3):265–7.
6. Donthireddy KR, Sikander A, Nasser E, Schiff MD, Nwogu CE, Nava HR, et al. Malignant gastroparesis: pathogenesis and management of an underrecognized disorder. J Support Oncol. 2007;4:355–63.
7. EPCRC Clinical Practice Guidelines on cancer cachexia. http://www.epcrc.org/publication_listfiles.php?id=mWdBCMI5eXVlcNFk7Gnq. Accessed 29 Sep 2016.
8. Wesseltoft-Rao N, Hjermstad MJ, Ikdahl T, Dajani O, Ulven SM, Iversen PO, et al. Comparing two classifications of cancer cachexia and their association with survival in patients with unresected pancreatic cancer. Nutr Cancer. 2015;67(3):472–80.
9. Fearon KC, Voss AC, Hustead DS. Cancer cachexia study group: definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr. 2006;83:1345–50.
10. Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane KW, Zabora JR. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics. 2009;50(4):383–91.
11. Clark KL, Loscalzo M, Trask PC, Zabora J, Philip EJ. Psychological distress in patients with pancreatic cancer—an understudied group. Psycho-Oncology. 2010;19:1313–20.
12. Endicott J. Measurement of depression in patients with cancer. Cancer. 1984;53(10 Suppl):S2243–9.
13. Periyakoil VS, Hallenbeck J. Identifying and managing preparatory grief and depression at the end of life. Am Fam Physician. 2002;65(5):883–90.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-5. Washington, DC: American Psychiatric Association; 2013.
15. Burris III HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15:2403–13.

16. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733–42.
17. Sohal DP, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34(23):2784–96.
18. Vyvey M. Steroids as pain relief adjuvants. Can Fam Physician. 2010;56:1295–7.
19. Bandieri E, Romero M, Ripamonti C, Artioli F, Sichetti D, Fanizza C, et al. Randomized trial of low-dose morphine versus weak opioids in moderate cancer pain. J Clin Oncol. 2016;34(5):436–42.
20. Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized double-blind study. J Clin Onol. 2004;22(1):185–92.
21. Mercadante S, Klepstad P, Kurita GP, Sjogren P. Giarratano on the behalf of The European Palliative Care Research Collaborative (EPCRC). Sympathetic blocks for visceral cancer pain management: a systematic review and EAPC recommendations. Crit Rev Oncol Hematol. 2015;96:577–83.
22. NCCN Clinical Practice Guidelines in Oncology Version 2.2016: Antiemesis. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 21 Oct 2016.
23. Bruera E, Belzile M, Neumann C, Harsanyi Z, Babul N, Darke A. A double-blind, crossover study of controlled-release metoclopramide and placebo for chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manag. 2000;19:427–35.
24. Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C. Phase II trial of mirtazapine for cancer-related cachexia and anorexia. Am J Hosp Palliat Med. 2010;27(2):106–10.
25. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J Clin Oncol. 1999;17:3299–306.
26. Greer JA, El-Jawahri AE, Pirl WF, Jackson VA, Park ER, Back A et al. Randomized trial of early integrated palliative and oncology care. J Clin Oncol 2016; 34(Suppl 26S): Abstr 104.
27. Walker J, Hansen CH, Martin P, Symeonides S, Gourley C, Wall L, et al. Integrated collaborative care for major depression comorbid with a poor prognosis cancer (SMaRT Oncology-3): a

multicentre randomised controlled trial in patients with lung cancer. Lancet Oncol. 2014;15:1168–76.
28. Williams S, Dale J. The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review. Br J Cancer. 2006;94:372–90.
29. Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. Cochrane Database of Systematic Reviews. 2015, Issue 6. Art. No.: CD011006.
30. Traeger L, Greer JA, Fernandez-Robles C, Temel JS, Pirl WF. Evidence-based treatment of anxiety in patients with cancer. J Clin Oncol. 2012;30:1197–205.

Chapter 14
Staging Diagnostic Laparoscopy for Localized Pancreatic Cancer

Raphael Louie and Kerrington Smith

Case Study

A 67-year-old Caucasian male was referred to the surgical oncology clinic for evaluation of a newly diagnosed pancreatic head mass. The patient initially presented to his primary care office 2 weeks ago for painless jaundice and 20-pound weight loss over the past 3 months. His past medical history is significant for hypertension and GERD. He has no prior surgical history. He smoked 1 pack/day of cigarettes for 30 years, but quit 5 years ago. The patient underwent ERCP and EUS a week ago, which found a 3.4 cm mass in the head of the pancreas. A plastic biliary stent was placed and the mass was biopsied under EUS. Cytology was consistent for adenocarcinoma. CT of the chest abdomen and pelvis confirmed a 3.4 cm mass at the head of the pancreas with <180° involvement of the portal vein. There is abutment to the

R. Louie, MD, MPH (✉) • K. Smith, MD
Department of Surgery, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Raphael.Louie@hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_14,

SMA but no celiac axis involvement. No distant metastases were seen. CA19-9 was 93. His total bilirubin was 0.7. On exam, this is a thin 67-year-old man, in no acute distress. No signs of jaundice at this time. His abdomen is soft, non-tender and non-distended.

My Management

A. Refer to palliative care.
B. Consent the patient for pancreaticoduodenectomy.
C. Refer to medical oncology for induction chemotherapy.
D. Consider induction chemotherapy with staging laparoscopy prior to surgical resection.

Diagnosis and Assessment

Pancreatic adenocarcinoma continues to be a devastating disease, with predicted overall 5-year survival rate of 7.7% [1]. Complete surgical resection (achieving a R0 resection) has a modest improvement in overall survival of 29% at 5 years. Unfortunately, only 15–20% of patients are demonstrated to be resectable at the time of presentation.

In this case presentation, this gentleman has had appropriate evaluation of his initial presenting symptom of painless jaundice. Evaluation included physical exam and appropriate laboratory work including liver function tests as well as a carbohydrate antigen (CA) 19-9. Next steps in evaluation include a CT of the chest, abdomen, and pelvis. Chest CT is recommended to rule out pulmonary metastases, while the abdominal and pelvis CT should undergo a pancreatic protocol. This protocol utilizes IV contrast with two delayed phases to capture visualization of the arterial flow along the celiac axis followed by a venous phase, which accentuates the portal venous system. Water rather than oral contrast is administered to dilate the small bowel to minimize artifact and enhance sensitivity in evaluating the pancreas.

Tissue diagnosis is important in establishing diagnosis of a pancreatic mass, as the underlying pathology can determine prognosis. The gold standard continues to be endoscopic ultrasound-guided FNA. Endoscopy can help further characterize the mass in terms of cystic components and size, provide information regarding vascular involvement, and obtain tissue for cytology and pathology. At the same time, ERCP may be utilized to selectively place stents in both the biliary and pancreatic systems to temporize obstructive symptoms. In the patient presented above, endoscopic intervention provided tissue diagnosis of a pancreatic adenocarcinoma while also providing therapeutic alleviation of his biliary and pancreatic obstruction.

In 2009, the American Hepato-Pancreato-Biliary Association, Society for Surgery of the Alimentary Tract, and Society of Surgical Oncology published a consensus statement providing parameters found on CT imaging to determine surgical resectability of pancreatic adenocarcinoma [2]. These criteria characterize pancreatic head masses in regard to resectability in relationship to vital vascular structures. Resectable disease is any pancreatic mass without involvement of the portal vein (PV), celiac axis, or superior mesenteric artery (SMA). Borderline resectable disease is defined as radiographic evidence of tumor-associated deformity of the SMV/PV, abutment of the SMV or PV greater than 180°, short segment occlusion of the SMV or PV amenable to resection and reconstruction, short segment of the hepatic artery involvement, or abutment of the SMA < 180°. Patients with more extensive tumor involvement were characterized as locally advanced disease (Table 14.1). Based on the imaging findings of this patient, he has borderline resectable, localized disease.

Management

As with any patients with a newly discovered pancreatic mass, imaging and tissue diagnosis would be important to establish a diagnosis. Tumor markers, specifically CA19-9,

Table 14.1 Adapted from 2009 American Hepato-Pancreato-Biliary Association, Society for Surgery of the Alimentary Tract, and Society of Surgical Oncology Consensus Definitions of Surgical Resectability of Pancreatic Adenocarcinoma [2]

Resectability	Definition
Resectable	• No tumor involvement of the SMA
	• Tumor abutment <180°
Borderline	• Tumor-associated deformity of the PV or SMV
	• Abutment of the SMV or PV ≥180°
	• Short segment occlusion of the SMV or PV amenable to resection or venous reconstruction
	• Short segment involvement of the hepatic artery or its branches amenable to resection or venous reconstruction
	• Abutment of the SMA (<180°)
Locally advanced	• Tumor encasement of the PV or SMV
	• Long segment occlusion of the SMV or PV not amenable to resection or venous reconstruction
	• Long segment involvement of the hepatic artery or its branches not amenable to resection or venous reconstruction
	• Abutment or encasement of the SMA (≥180°)

should be obtained. It must be noted that 5–10% of patients can have a false negative due to do not produce CA19-9, as most common in patients Lewis-negative phenotpyes [3]. Additionally, patients with obstructive jaundice may exhibit an elevated CA19-9. In the patient presented, tissue diagnosis has confirmed the underlying pathology. Based on imaging

criteria, this patient has borderline resectable disease, without overt evidence of metastatic disease. As mentioned in prior chapters, surgery currently continues to be the main means of providing a chance of cure. It must be noted that 5–15% of patients without radiographic evidence of metastatic disease have occult disease at the time of surgery. Exploratory laparotomy has its own risks and morbidity associated with the operation, in which staging or diagnostic laparoscopy may reduce the morbidity and costs associated with an aborted laparotomy.

Current National Comprehensive Cancer Network guidelines recommend staging laparoscopy as an adjunct to accurately stage patients with pancreatic adenocarcinoma, specifically patients with high-risk characteristics: borderline resectability, large primary tumors, bulky lymphadenopathy, highly elevated CA19-9, and/or extreme weight loss. Staging laparoscopy should be performed prior to exploration for surgical intent. Under general anesthesia, access to the abdomen can be obtained according to surgeon preference. Typically a periumbilical port for either a 5 or 10 mm 30° laparoscope would be placed first. This allows a good survey of the entire abdominal cavity. One or two additional 5 mm ports can be placed after surveying the abdomen for optimal port placement. Careful examination of the liver surface, falciform ligament, and peritoneal lining should be performed. Trocars should be placed to facilitate evaluation of the undersurface of the liver. Suspicious nodules should be biopsied and sent to pathology to evaluate for malignancy. Currently, there are no standardized steps; however, some surgeons have advocated for an extended procedure by accessing the lesser sac laparoscopically [4]. In the setting of neoadjuvant chemoradiation for borderline resectable and locally advanced adenocarcinoma, staging laparoscopy prior to initiating neoadjuvant therapy may allow to accurately stage patients with underlying metastatic disease.

Outcome

The patient underwent scheduled staging laparoscopy. At the time of the operation, a 5 mm white nodule was identified on the anterior surface of segment V. A wedge biopsy was obtained, and pathology confirmed adenocarcinoma consistent with pancreatic etiology. The patient was referred to medical oncology for chemotherapy treatment options.

Staging laparoscopy has been advocated as an adjunct in the workup of patients with pancreatic adenocarcinoma since the 2000s. Despite advances in radiographic imaging over the last several years, staging laparoscopy continues to provide a valuable tool in the detection of metastatic disease. Allen and colleagues published a 2016 Cochrane review addressing the accuracy of staging CT and staging laparoscopy. The review included 16 studies that included 1146 patients. The meta-analysis demonstrated that patients with CT scans had a pretest probability of 41.1% with radiographic occult metastatic disease. The posttest probability following staging laparoscopy decreased to 20% [5].

Proponents of staging laparoscopy have long argued that the detection of occult metastatic disease with staging laparoscopy can offset the surgery-associated morbidity that the patient may incur with surgery first laparotomy and expedite the initiation of systemic chemotherapy. To quantify the benefits of staging laparoscopy, one study in the UK and one study in the USA assessed the cost-effectiveness of the procedure.

Morris and colleagues evaluated the costs in relation to QALYs within the National Health System and found that in incurred costs between staging laparoscopy and upfront laparotomy, there was a significant improvement in mean quality-adjusted life-years in the staging laparoscopy group [6]. In a similar study conducted in the USA, Jayakrishnan and colleagues again demonstrated improved quality-adjusted life-months in patients undergoing staging laparoscopy, particularly in patients qualifying for neoadjuvant chemotherapy [7].

Both of these studies quantified the differences in hospital stay and associated morbidity of staging laparoscopy in comparison to surgery first options.

Clinical Pearls/Pitfalls

- Staging laparoscopy in pancreatic adenocarcinoma currently improves the detection of occult metastatic disease.
- Consider staging laparoscopy in patients with localized borderline resectable tumors.
- Staging laparoscopy is a cost-effective measure to avoid morbidity associated with exploratory laparotomy as the initial modality for surgical management of pancreatic adenocarcinomas.

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER cancer statistics review, 1975–2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER. Accessed Apr 2016.
2. Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1751–6.
3. Ballehaninna U, Chamberlain R. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol. 2012;3(2):105–19.
4. Schnelldorfer T, Gagnon AI, Birkett RT, Reynolds G, Murphy KM, Jenkins RL. Staging laparoscopy in pancreatic cancer: a potential role for advanced laparoscopic techniques. J Am Coll Surg. 2014;218(6):1201–6.

5. Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2016;7:CD009323.
6. Morris S, Gurusamy KS, Sheringham J, Davidson BR. Cost-effectiveness of diagnostic laparoscopy for assessing resectability in pancreatic and periampullary cancer. BMC Gastroenterol. 2015;15:44.
7. Jayakrishnan TT, Nadeem H, Groeschl RT, George B, Thomas JP, Ritch PS, Christians KK, Tsai S, Evans DB, Pappas SG, Gamblin TC, Turaga KK. Diagnostic laparoscopy should be performed before definitive resection for pancreatic cancer: a financial argument. HPB (Oxford). 2015;17(2):131–9.

Chapter 15
Neoadjuvant Multimodality Therapy for Borderline Resectable Pancreatic Head Cancer

Maureen V. Hill and Kerrington D. Smith

Case Study

Sixty-two-year-old female presented with a 2-week history of abdominal pain. Work-up included a right upper quadrant ultrasound, CT scan of the abdomen/pelvis, and MRCP that revealed a pancreatic head mass and a dilated pancreatic duct. She subsequently underwent ERCP with pancreatic stent placement. Two weeks later, an endoscopic ultrasound was performed where a 24 × 28 mm pancreatic head mass was confirmed. FNA was performed at this time and confirmed pancreatic adenocarcinoma. She underwent repeat CT scan of the abdomen/pelvis and chest where no metastatic disease was noted.

After a case review at a multidisciplinary tumor board, her tumor was designated at "borderline resectable" as there was $a < 180°$ abutment on the portal vein causing mild narrowing. It was recommended that she undergo diagnostic laparoscopy

M.V. Hill, MD (✉) • K.D. Smith, MD
Department of Surgery, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03784, USA
e-mail: Maureen.v.hill@hithcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_15,

for staging and subsequent neo-adjuvant chemotherapy. Diagnostic laparoscopy was negative for metastatic disease, and she initiated neoadjuvant therapy (gemcitabine/Abraxane × 2 cycles and twice weekly gemcitabine with concurrent radiation).

She completed her treatment 6 months after diagnosis. Restaging CT scan revealed a decrease in size in her primary tumor with less abutment on the portal vein and no evidence of metastatic disease.

My Management

1. I would proceed with diagnostic laparoscopy and continue to definitive surgical management only after consideration of neoadjuvant treatment.

Diagnosis and Assessment

To assess for a possible pancreatic tumor, the National Comprehensive Cancer Network (NCCN) recommends obtaining a multidetector computerized tomography (CT) scan using a pancreatic protocol [1]. This "triple-phase" CT ensures thin cut (5–10 mm) images obtained in the non-contrast, arterial phase and pancreatic parenchyma/portal venous contrast phases in addition to a low-density oral contrast. This protocol assists in visualizing the tumor and the surrounding vasculature, as assessing its relationship to the vessels (which include the portal vein, splenic vein, superior mesenteric vein and artery, celiac axis, and gastroduodenal artery (GDA)) helps determine resectability. A pancreas protocol CT scan has good sensitivity (89–97%) and negative predictive value [2] in detecting a pancreatic mass. In addition to assessing the pancreas and its surrounding structures, this imaging study has the capability of ruling out metastatic disease. A magnetic resonance imaging (MRI) study could be performed if the patient was unable to obtain a CT scan.

Once there is suspicion of a pancreatic tumor on CT scan, endoscopic ultrasound (EUS) is generally performed to further characterize the lesion as well as to obtain a tissue diagnosis [3]. If the patient is to obtain neoadjuvant treatment, this tissue biopsy is imperative. In addition, a therapeutic endoscopic cholangiopancreatography (ERCP) procedure can be performed in the same setting if the patient is demonstrating signs of biliary or pancreatic duct obstruction [3].

When assessing the primary tumor, it is imperative to assess its relationship to surrounding vascular structures and its resectability, as resectability helps determine treatment strategies. Historically, the term "borderline" was used to describe those patients who had a high risk of a positive surgical margin secondary to the anatomic relationship of the tumor to vessels. Many different definitions have been described and used in the literature, therefore making comparing studies and outcomes difficult. The National Comprehensive Cancer Network (NCCN) and the International Study Group of Pancreatic Surgery (ISGPS) define borderline resectable pancreatic cancer (BRPC) as CT findings of venous distortion of the SMV/portal venous axis even including short-segment venous occlusion with proximal and distal sufficient vessel length allowing safe reconstruction; encasement of the gastroduodenal artery up to the hepatic artery, with either short-segment encasement or direct abutment of the hepatic artery without extension to the celiac axis; and tumor abutment of the SMA but with no greater than 180° of the vessel wall circumference.

Further metastatic staging should be performed in these patients regardless of whether there is metastatic disease present in the abdomen. A CT of the chest will suffice. Obtaining a positron-emission tomography (PET) scan is controversial, and currently there are no strong recommendations to obtain this [3]. In patients who are high risk for occult metastatic disease, a staging laparoscopy is recommended. Most institutions only perform staging laparoscopy on patients with a resectable tumor [4], as the presence of metastatic disease would change management on these

patients. However, if the patient is going directly to surgery or if their chemotherapy treatment strategy would differ if they had metastatic disease, a staging laparoscopy in borderline or locally advanced patients is indicated.

In addition, a CA 19-9 level should also be performed at diagnosis as this marker can be followed throughout treatment to assist in grading response or progression/recurrence [5]. This level should only be checked in the setting of a decompressed biliary system, as hyperbilirubinemia increases CA 19-9 levels [6].

Management

When deciding the management strategy for a patient, a multidisciplinary collaboration by oncologists, radiation oncologists, and pancreatic surgeons is imperative [7]. Despite the growing range of treatment modalities, surgical excision remains the definitive treatment and is the only cure [8]. Therefore, the goal for patients with borderline resectable cancer is to increase their odds of an R0 (pathologic negative margin) surgical resection. This may be difficult up front in patients with BRPC due to the potential vascular involvement and the high likelihood of leaving microscopic disease along the vascular margins.

Neoadjuvant therapy (either chemotherapy only or chemoradiation) continues to be controversial in the treatment of borderline resectable cancers. The role of neoadjuvant therapy in this group is to assist in achieving an R0 resection. It has been shown to slightly increase postoperative leak and fistula rates [9] and anecdotally make the resection itself more difficult secondary to scaring, making it therefore unfavorable to some centers [10]. In addition the effect that neoadjuvant therapy has on local and distant recurrence remains mixed [11–13]. Neoadjuvant therapy, however, does treat microscopic and micro-metastatic disease therefore increasing the rate of negative margins during resection. In addition, it can also help gauge how aggressive the patients'

tumor is. If a patient progresses on neoadjuvant therapy, they are not likely to have a favorable outcome. This could save them the morbidity of undergoing a pancreatic resection. It is for these reasons that most large cancer centers have continued with this treatment strategy [14].

Currently the NCCN recommends FOLFIRINOX as a primary neoadjuvant chemotherapeutic agent; however, there are few prospective trials looking at the effect of FOLFIRINOX in the treatment of BRPC. There is strong prospective data that shows improved survival in the setting of metastatic pancreatic cancer and retrospective data for locally advanced cancer [15]. The Alliance trial (A021101) is currently enrolling to evaluate the effect of FOLFIRINOX followed by capecitabine-based chemoradiation for patients with BRPC. Other treatment strategies in the neoadjuvant setting include gemcitabine- or paclitaxel-based therapies. Gemcitabine is typically used in addition to radiotherapy, and secondary to improved median survival, gemcitabine-based radiotherapy is becoming widely accepted [3].

The use of radiation in addition to chemotherapy in neoadjuvant therapy is also controversial. There is currently no standard radiotherapy treatment regimen for borderline resectable pancreatic cancer; however, treatment strategies are usually similar to those given for locally advanced disease, which is gemcitabine-based chemoradiation. All decisions on modality and dosing should be made in conjunction with radiation and clinical oncologists.

When (if) the patient has completed neoadjuvant therapy, a restaging CT scan is performed prior to definitive surgery. A post-treatment CA 19-9 level should also be checked. If there is evidence of stability or response in their tumor, with no other signs or symptoms of systemic disease, and they continue to be medically fit, they can proceed to surgical resection. The goal is to perform an R0 resection, and if necessary, vascular reconstruction may need to be performed in addition to the standard pancreaticoduodenectomy or distal pancreatectomy.

Outcome

Eight weeks after completion of neoadjuvant therapy, the patient underwent a successful pancreaticoduodenectomy without the need for vascular reconstruction. Pathology revealed a 2.2 cm tumor, R0 resection, negative lymph nodes (0/6), and a moderate pathologic treatment response (pT3N0).

Clinical Pearls/Pitfalls

- The definition of borderline pancreatic cancer is CT findings of venous distortion of the SMV/portal venous axis even including short-segment venous occlusion with proximal and distal sufficient vessel length allowing safe reconstruction; encasement of the gastroduodenal artery up to the hepatic artery, with either short-segment encasement or direct abutment of the hepatic artery without extension to the celiac axis; and tumor abutment of the SMA but with no greater than 180° of the vessel wall circumference.
- A multidisciplinary team approach is key in treating these patients.
- Most centers recommend neoadjuvant chemotherapy for treatment of these tumors; however, the role of neoadjuvant radiotherapy remains controversial.
- Despite the growing evidence and continued debate of the role of chemo- and radiotherapy in the treatment of pancreatic cancer, surgery remains the only definitive treatment.

References

1. Clinical practice guidelines in oncology. In: Pancreatic adenocarcinoma. National Comprehensive Cancer Network. 2016. http://www.nccn.org/progessional/physician_gls/pdf/pancreatic. Accessed 1 Apr 2016.

2. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol. 2008; 6:1301–1308. doi: 10.10/j.cgh.2008.09.014
3. Katz MH, Crane CH, Varadhacery G. Management of borderline resectable pancreatic cancer. Semin Radiat Oncol. 2014;24:105–12. doi:10.1016/j.semradonc.2013:11.006.
4. DeRosa A, Cameron IC, Gomez D. Indications for staging laparoscopy in pancreatic cancer. HPB. 2016;18:13–20. doi:10.1016/j.hpb.2015.10.004.
5. Ritts RE, Pitt HA. CA 19-9 in pancreatic cancer. Surg Oncol Clin N Am. 1998;7:93–101.
6. Mann DV, Edwards R, Ho S, Lau WY, Glazer G. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol. 2000;26:474–9.
7. Schwarz L, Katz MH. Diagnosis and management of borderline resectable pancreatic adenocarcinoma. Hematol Oncol Clin N Am. 2015;29:727–40. doi:10.1016/j.hoc.2015.04.004.
8. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg. 2000;4:567–79.
9. Verma V, Li J, Lin C. Neoadjuvant therapy for pancreatic cancer: A systematic review of postoperative morbidity, mortality and complications. Am J Clin Oncol. 2016;39(3):302–13. doi:10.1097/COC. 0000000000000278.
10. Cho SW, Tzeng CW, Johnston WC, Cassera MA, et al. Neoadjuvant radiation therapy and its impact on complications after pancreaticoduodenectomy for pancreatic cancer: analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). HPB. 2014;16(4):350–6.
11. Papavasiliou P, Hoffman JP, Cohen SJ, et al. Impact of preoperative therapy on patterns of recurrence in pancreatic cancer. HPB. 2014;16(1):34–9. doi:10.1111/hpb.12058.
12. Hishinuma S, Ogata Y, Tomikawa M, et al. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy results. J Gastrointest Surg. 2006;10:511–8.
13. Greer SE, Pipas JM, Sutton JE, et al. Effect of neoadjuvant therapy on local recurrence rates after resection of pancreatic adenocarcinoma. J Am Coll Surg. 2008;206:451–7. doi:10.1016/j.jamcollsurg.2007.10.002.
14. Abrams RA, Lowy AM, O'Reilly EM, et al. Combined modality treatment of resectable and borderline resectable pancreas cancer:

expert consensus statement. Ann Surg Oncol. 2009;16:1751–6. doi:10.1245/s10434-009-0413-9.
15. Conroy T, Desseigne G, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25. doi:10.1056/NEJMoa1011923.

Chapter 16
Drainage and Resection Surgery for Pancreatitis

Samuel J. Kesseli, Kerrington D. Smith, and Timothy B. Gardner

Abbreviations

PERT Pancreatic enzyme replacement therapy

Samuel.J. Kesseli, BS
Geisel School of Medicine at Dartmouth,
1 Rope Ferry Road,
Hanover, NH 03755, USA
e-mail: Samuel.J.Kesseli.MED@Dartmouth.edu

T.B. Gardner, MD
Section of Gastroenterology and Hepatology,
Dartmouth-Hitchcock Medical Center,
One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.B.Gardner@Hitchcock.org

K.D. Smith
Department of Surgery, Dartmouth-Hitchcock Medical Center,
One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Kerrington.D.Smith@Hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_16,

Case Study

A 70-year-old man with a 6-month history of progressive alcoholic chronic pancreatitis and exocrine insufficiency presents to the office for surgical evaluation. Five months ago he initiated pancreatic enzyme replacement therapy (PERT) and has since seen a dramatic reduction in postprandial abdominal pain; he seldom requires narcotic analgesia. His primary concern is that he continues to experience loose greasy stools up to four times daily and has lost 50 pounds in the past year.

His past medical history is otherwise unremarkable and he is nondiabetic. Current medications include a pancreatic enzyme preparation and oxycodone as needed for abdominal pain. Exam in clinic demonstrates a thin, non-icteric man in no acute

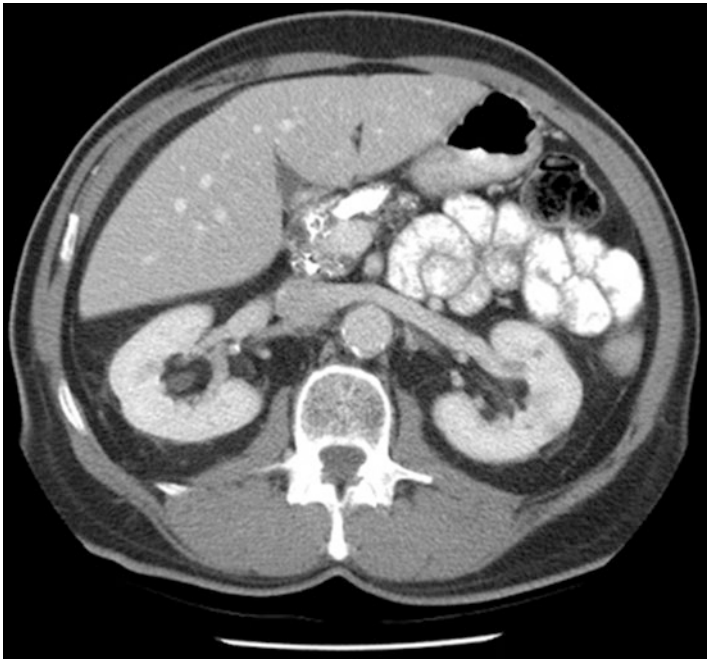

Figure 16.1 Computed Tomography scan demonstrating chronic pancreatitis with diffuse parenchymal calcifications. A large stone within the pancreatic head is seen occluding the duct of Wirsung

distress and vital signs within the normal range. His abdomen is non-tender with no palpable masses, hernias, or organomegaly.

A recent abdominal CT scan (Fig. 16.1) confirmed the diagnoses of diffuse calcific pancreatitis and also revealed significant pancreatic duct dilation to 10 mm and multiple intraductal stones. Additionally, CT revealed variant hepatic arterial anatomy, with a complete replaced right hepatic artery from the superior mesenteric artery, which passes through the head of the pancreas.

My Management

1. Proceed to pancreatic drainage surgery.

Diagnosis and Assessment

Surgical intervention for chronic pancreatitis is indicated in patients with persistent symptoms despite medical therapy, those with severe calcific disease, or those with distal obstructions not amenable to endoscopic drainage. Given that this patient has evidence of multiple intraductal obstructions and is having significant weight loss and steatorrhea while on PERT, he may benefit from drainage or resection surgery.

The following list summarizes commonly used surgical approaches to pancreatitis.

The Puestow Procedure

The Puestow procedure, also known as a longitudinal pancreaticojejunostomy, is a drainage operation in which a side-to-side anastomosis is made between a longitudinal pancreatic ductotomy and a Roux-en-Y limb of the jejunum [1]. The Puestow procedure is used in patients with diffuse ductal dilation (>7 mm) and confers little benefit to patients with nondilated ducts [2, 3]. With regard to endocrine function, 27–29% of patients will develop new-onset diabetes mellitus postoperatively [4, 5]. One common criticism of the Puestow procedure is that pain relief is suboptimal, with 15–20% of

patients having no immediate pain relief and an additional 20% develop recurrence of pain years after the procedure [6]. Small cohort studies have suggested that 7–21% [4, 7] of patients will eventually require a salvage excisional procedure due to progressive parenchymal disease and pain.

The Beger Procedure

The Beger procedure is commonly referred to as duodenum-preserving pancreatic head resection. In this operation, the pancreas is transected at the level of the portal vein, and the head is removed while preserving the bile duct. The distal pancreatic remnant is then drained into a Roux limb of the jejunum. The Beger operation is indicated in head-predominant pancreatic disease, such as pancreatitis secondary to inflammatory masses or obstructive ductal neoplasia [8]. The primary advantage over a classic Whipple pancreaticoduodenectomy is that both the endocrine and mechanical properties of the duodenum implicated in gastric emptying are preserved. In a long-term follow-up study of 388 patients by Beger et al., greater than 90% had pain relief, and about 11% were found to have improvement in their endocrine function; 21% developed diabetes following the procedure [9].

The Frey Procedure

The Frey procedure combines localized pancreatic head resection with a longitudinal pancreaticojejunostomy; it is essentially a hybrid operation that incorporates aspects of both the Puestow and Beger procedures. It is therefore ideal in patients with significant disease of the pancreatic head that also extends into the ductal system. A major advantage of the Frey procedure is that it enables surgeons to perform a complete decompression of the ductal system with particular attention to the duct of Santorini and the duct to the uncinate; these may otherwise be incompletely decompressed during a traditional Puestow procedure. In addition, the Frey

procedure incurs lower operative risk compared to the Beger head resection, because the pancreas is not transected above the portal vein, but instead the posterior capsule of the pancreas is left intact [10]. Numerous studies have concluded that the degree of pain relief is comparable to that seen with the Beger procedure, with some degree of relief in >90% of patients [11–13].

Distal Pancreatectomy

Distal pancreatectomy is less commonly employed for the treatment of chronic pancreatitis, but may be indicated in cases of body- or tail-predominant disease. The border of resection is patient specific, but typically about 50% of the total pancreatic volume is removed. Due to the shared splenic vasculature, the pancreatic tail is removed with the spleen en bloc. Pain relief is less robust compared with alternate surgical methods, with only 60–88% of patients having improvement in their pain [14, 15]. Additionally, given the relatively large parenchymal resection associated with distal pancreatectomy and the increased islet cell density in the tail relative to the head [16], development of diabetes is of particular concern in distal pancreatectomy patients; Hutchins et al. found that 46% of their cohort developed diabetes mellitus postoperatively [15].

Total Pancreatectomy

Though drastic, total pancreatectomy is indicated for the treatment of chronic pancreatitis in patients with diffuse, non-focal disease that would not be responsive to a partial resection procedure. This is often a last resort operation reserved for the most severe cases of pancreatitis, given that in excising the entire pancreas, both endocrine and exocrine function are permanently compromised. A “completion” total pancreatectomy may also be performed as a salvage operation in patients who continue to have pain following

partial resections. Recently, there has been considerable interest in the application of autologous islet cell transplantation following total pancreatectomy to reduce the burden of surgical diabetes. With islet autotransplant, approximately one-third of total pancreatectomy patients are insulin-free following the procedure. For more information on islet cell transplantation, see Chap. 17.

Pertinent factors in selecting the optimal drainage or resection procedure for this patient include his:

- Degree of ductal dilation and obstruction
- Intact endocrine function
- Minimal baseline pain
- Abnormal arterial anatomy

With these considerations, the Puestow procedure is a reasonable intervention. First, it will effectively relieve his ductal obstruction by allowing the removal and passage of stones. Second, it incurs a relatively low risk of compromising his endocrine function given the minimal parenchymal resection. Third, because he has minimal pain at baseline, the durability of pain relief associated with the Puestow is of less concern. Lastly, the Puestow procedure will reduce the risk of injury to the replaced hepatic artery present in the head of his pancreas.

Management

Operative Procedure

Upon establishing exposure to the pancreas, the pancreatic duct can be identified from the inferior border by inserting a needle and aspirating pancreatic fluid. Once localized, the duct can be fileted open with electrocautery extending first toward the tail and then rightward toward the neck of the pancreas (Fig. 16.2). Intraductal stones can then be manually disimpacted and removed. The jejunum is divided 10–30 cm distal to the ligament of Treitz, and a Roux limb of about 50 cm can be brought up to comprise the pancreaticojejunostomy. About 5 cm of the

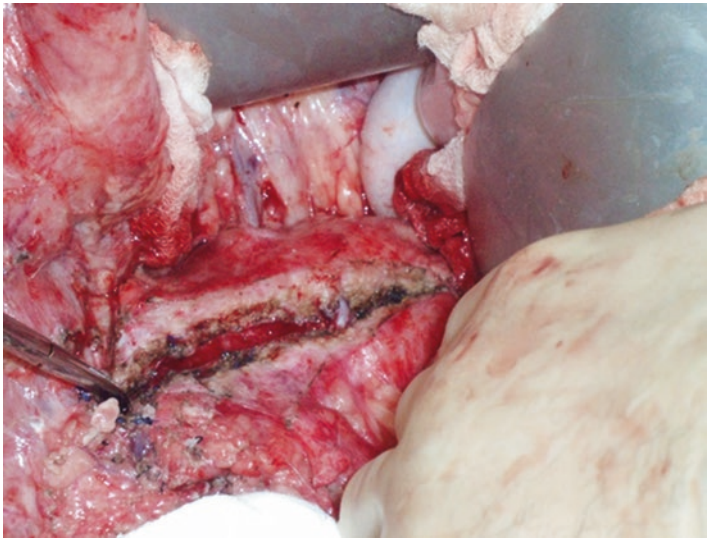

FIGURE 16.2 Intraoperative photo of the dilated main pancreatic duct

jejunum on the Roux limb should be opened opposite the mesentery. The side-to-side anastomosis is then made with full thickness duct-to-mucosa interrupted stiches from left to right. The anastomosis can be tested for leaks with saline submersion. The jejuno-jejunal anastomosis can then be created with the surgeon's preferred method approximately 50 cm distal to the pancreaticojejunostomy. Before closing, a drain can be placed in Morrison's pouch to monitor output during recovery.

Postoperative Considerations

- Blood glucose—In anticipation of altered pancreatic function, we recommend once daily blood glucose checks prior to breakfast and use of an insulin sliding scale.
- Nutrition—An oral diet can typically be initiated within the first few postoperative days as bowel function returns. We recommend a low-fat diet with vitamin supplementation. Patients should expect to remain on PERT.

- Drain output—To monitor for anastomotic leak, we recommend daily drain and serum amylase measurement. A drain/serum amylase ratio greater than 3 and/or fluid output >50 ml per day may raise clinical suspicion of anastomotic leak [17].

Outcome

At his routine 1-month follow-up visit, the patient is no longer having loose, greasy stools, and denies any symptoms of nausea, vomiting, bloating, or diarrhea. He is averaging one bowel movement per day. He continues to take PERT three times daily with meals. Blood glucose values range from 100 to 140 s on 10 units of insulin twice daily, and he requires minimal narcotics as needed for postsurgical pain.

Clinical Pearls/Pitfalls

- Drainage and resection surgery is indicated in pancreatitis that fails medical and endoscopic therapy.
- The Puestow procedure is useful in patients with symptomatic intraductal obstruction.
- The Beger and Frey procedures offer excellent pain reduction for patients with head-predominant pancreatitis.
- Postoperative diabetes mellitus is a risk in all drainage and resection surgery, but the risk is highest with distal or total pancreatectomy.

References

1. Adams DB. The Puestow procedure: how I do it. J Gastrointest Surg. 2013;17(6):1138–42.
2. Rios GA, et al. Outcome of lateral pancreaticojejunostomy in the management of chronic pancreatitis with nondilated pancreatic ducts. J Gastrointest Surg. 1998;2(3):223–9.

3. Strobel O, Büchler MW, Werner J. Surgical therapy of chronic pancreatitis: indications, techniques and results. Int J Surg. 2009;7(4):305–12.
4. Adams DB, Ford MC, Anderson MC. Outcome after lateral pancreaticojejunostomy for chronic pancreatitis. Ann Surg. 1994;219(5):481.
5. Schnelldorfer T, Lewin DN, Adams DB. Operative management of chronic pancreatitis: longterm results in 372 patients. J Am Coll Surg. 2007;204(5):1039–45.
6. Markowitz JS, Rattner DW, Warshaw AL. Failure of symptomatic relief after pancreaticojejunal decompression for chronic pancreatitis: strategies for salvage. Arch Surg. 1994;129(4):374–80.
7. Dhar VK, et al. The natural history of chronic pancreatitis after operative intervention: The need for revisional operation. Surgery. 2016;160(4):977–86.
8. Beger HG, Kunz R, Poch B. The Beger procedure—duodenum-preserving pancreatic head resection. J Gastrointest Surg. 2004;8(8):1090–7.
9. Ho HS, Frey CF. The Frey procedure: local resection of pancreatic head combined with lateral pancreaticojejunostomy. Arch Surg. 2001;136(12):1353–8.
10. Frey CF, Mayer KL. Comparison of local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy (Frey procedure) and duodenum-preserving resection of the pancreatic head (Beger procedure). World J Surg. 2003;27(11):1217–30.
11. Strate T, et al. Long-term follow-up of a randomized trial comparing the Beger and Frey procedures for patients suffering from chronic pancreatitis. Ann Surg. 2005;241(4):591–8.
12. Pessaux P, et al. Frey procedure in the treatment of chronic pancreatitis: short-term results. Pancreas. 2006;33(4):354–8.
13. Hutchins RR, et al. Long-term results of distal pancreatectomy for chronic pancreatitis in 90 patients. Ann Surg. 2002;236(5):612–8.
14. Wang X, et al. Regional differences in islet distribution in the human pancreas-preferential beta-cell loss in the head region in patients with type 2 diabetes. PLoS One. 2013;8(6):e67454.
15. Crippa S, et al. Anastomotic leakage in pancreatic surgery. HPB. 2007;9(1):8–15.
16. Beger HG, et al. Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease: a single-center 26-year experience. Ann Surg. 1999;230(4):512.
17. Schoenberg MH, et al. Distal pancreatectomy in chronic pancreatitis. Dig Surg. 1999;16(2):130–6.

Chapter 17
Pancreatectomy with Islet Autotransplant

Samuel J. Kesseli, Kerrington D. Smith, and Timothy B. Gardner

Abbreviations

CFTR	Cystic fibrosis transmembrane conductance regulator
MRCP	Magnetic resonance cholangiopancreatography
PRSS1	Protease serine 1

S.J. Kesseli, BS (✉)
Geisel School of Medicine at Dartmouth,
1 Rope Ferry Road, Hanover, NH 03755, USA
e-mail: Samuel.J.Kesseli.MED@Dartmouth.edu

K.D. Smith, MD
Department of Surgery, Dartmouth-Hitchcock
Medical Center, One Medical Center Drive,
Lebanon, NH 03756, USA
e-mail: Kerrington.D.Smith@Hitchcock.org

T.B. Gardner, MD
Section of Gastroenterology and Hepatology,
Dartmouth-Hitchcock Medical Center,
One Medical Center Drive, Lebanon, NH 03766, USA
e-mail: Timothy.B.Gardner@Hitchcock.org

T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8_17,

SPINK1	Serine protease inhibitor Kazal-type 1
TP-IAT	Total pancreatectomy with islet autotransplant
TPN	Total parenteral nutrition

Case Study

A 16-year-old male presents to the office for follow-up of CFTR-induced pancreatitis. His past medical history is notable for multiple hospital admissions for bouts of pancreatitis characterized by severe abdominal pain, nausea, vomiting, and diarrhea. Review of his medical record demonstrates he recently underwent MRCP that revealed pancreatic divisum and diffuse pancreatic atrophy. He has no history of alcohol or tobacco use, hypertriglyceridemia, or gallstones. A genetic panel was positive for the delta F508 CFTR mutation, but negative for PRSS1 or SPINK1 mutations. Currently, pancreatitis is the only manifestation of his cystic fibrosis; workup for pulmonary disease, liver disease, and infertility were unremarkable.

Following his last admission 2 months ago, he was started on pancreatic enzyme replacement therapy, but today reports it has not alleviated his symptoms of nausea, vomiting, and epigastric pain. While he previously had intermittent pain, for the past month it has been constant. The pain radiates to his back and is exacerbated by eating or drinking. His current daily medications include ondansetron 4 mg, diphenoxylate-atropine 2.5–0.025 mg, and oxycodone 10 mg, all of which are transiently helpful in symptom management. As a result of his debilitating symptoms, he is more than 1 year behind in high school.

Physical exam reveals an overweight boy in no acute distress, with blood pressure 156/94 mmHg, pulse 80 bpm, and BMI 34. His abdomen is slightly distended and is moderately tender to deep palpation diffusely. No guarding or peritoneal signs are present. No hepatosplenomegaly or palpable masses are appreciated. The remainder of the exam is unremarkable. Labs are notable for a lipase of 120 μ/L. A CBC, CMP, and LFTs are within normal limits.

My Management

1. Hydration and narcotic analgesia as needed to manage current flare
2. Multidisciplinary evaluation for total pancreatectomy with islet autotransplant
3. Abdominal CT for surgical planning

Diagnosis and Assessment

This patient demonstrates progressive, diffuse chronic pancreatitis secondary to CFTR mutation and pancreatic divisum. Given that there are no reversible causes to his pancreatitis and that he is not responding to medical therapy, he may benefit from surgical intervention. While several surgical options exist, only a total pancreatectomy with islet autotransplant (TP-IAT) can fully eliminate the source of his pain without compromising pancreatic endocrine function.

TP-IAT is a novel procedure that involves digestion of the explanted pancreas and isolation of the patient's islet cells, which can be reimplanted into the liver, peritoneum, or other heterotopic sites. Upon implantation, a fraction of the islet cells remain viable and responsive to patients' natural glucose excursions. Based on the largest series of TP-IAT patients to date, pain improvement is seen in 85% of patients, and about one-third of patients achieve complete insulin independence following the procedure [1]. Interestingly, studies have reported superior outcomes in pediatric populations, and a younger age is associated with a higher likelihood of achieving postoperative insulin independence [2].

Management

To qualify the patient for TP-IAT, several criteria should be met to ensure an optimal outcome. We evaluate the patient with a multidisciplinary team that includes a pancreatologist, pancreatic surgeon, transplant surgeon, endocrinologist, and social worker. Five criteria must be met for approval:

Patient selection criteria for TP-IAT.

Criterion	Examples
Poor response to maximal medical therapy	Pancreatic enzyme replacement therapy, opiate analgesics, endoscopic decompression
Preserved islet cell function	Nondiabetic, C-peptide positive diabetes
Debilitating pain	Severe and intermittent vs. moderate and chronic
Diminished quality of life	Unable to attend work or school, difficulty with activities of daily living
No contraindications	Active drug or alcohol abuse, known malignancy, severe psychiatric issues

Preoperative Preparation

In preparation for the procedure, patients should meet with the endocrinology team to establish baseline endocrine function and to receive diabetes education, as they will require an insulin taper following the surgery as the islet cells recover. A referral with the transplant surgery team should also be made to review the procedure risks as well as receive prophylactic vaccination in anticipation of the splenectomy that will occur with removal of the pancreas; these include the pneumococcal, H. Influenza type b, meningococcal, and annual influenza immunizations [3].

Operative Procedure

Technical aspects of the procedure will vary depending on the patient's prior surgical history as well as the performing surgeon. In general, pancreatectomy for TP-IAT is unique in that blood flow to the organ must be preserved throughout the dissection to minimize warm ischemia time [4]. The spleen is removed with the distal pancreas, while the head and uncinate can be removed en bloc with duodenum, antrum, and distal portions of bile duct. Following explant, the organ is placed in static preservation solution to be prepped for islet isolation (Fig. 17.1). While some centers are equipped to perform the isolation intraoperatively,

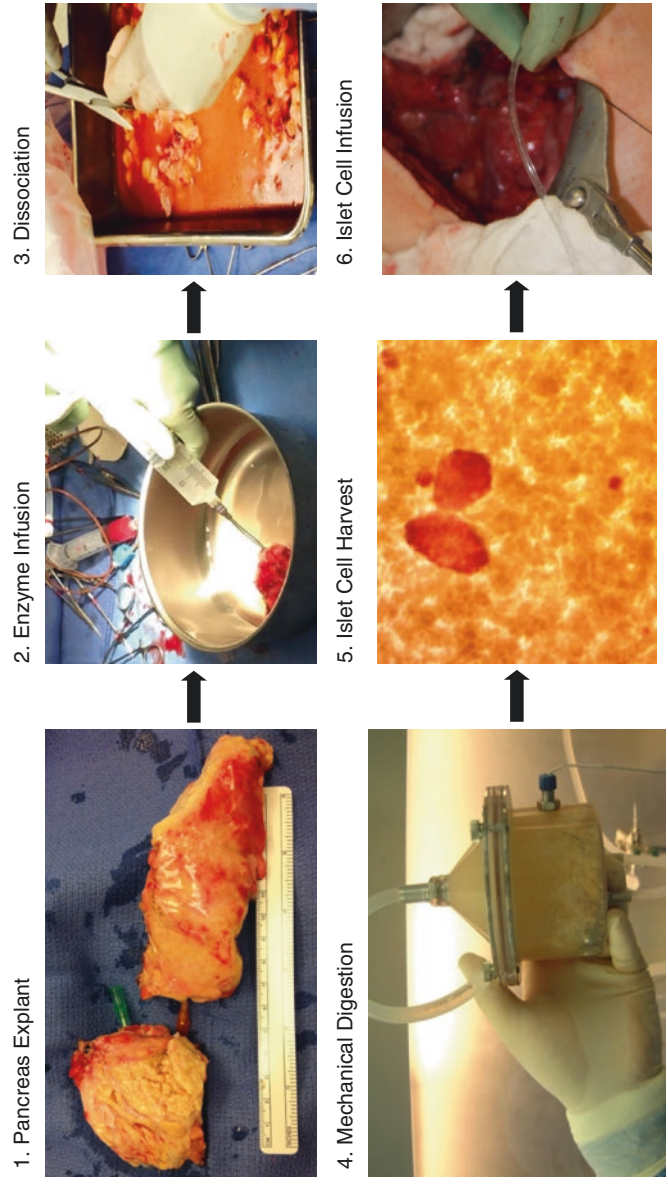

FIGURE 17.1 Schematic representation of the islet cell isolation process

others may need to ship the preserved organ to a remote facility. The isolated islet suspension is then infused directly into the portal vein with heparin. Portal pressures should be measured throughout the infusion to minimize the risk of thrombosis, which becomes significantly elevated if pressures exceed 25 mm H_2O [5]. If maximal pressures prevent completion of portal vein infusion, excess islets can be injected into the omentum or peritoneum; these sites also enable engraftment, but to date, the portal vein remains the gold standard for islet infusion [6]. Lastly, we prefer to place a jejunostomy tube for enteral feeding as this can reduce rates of readmission, vomiting, and use of TPN, though comes with the risk of increased morbidity related to site infection and other complications [7, 8].

Postoperative Management

Postoperatively, patients will require strict glucose monitoring and control, as hyperglycemia has been shown to decrease beta cell graft mass in islet cell transplanted animal models [9]. Fingerstick blood glucose should be evaluated every hour, with a target range of 80–130 mg/dL. Nearly all patients will require an insulin drip during this phase, typically at rates between 1.0 and 3.0 units/h. Additionally, sliding scale bolus may be required with each tube feed to prevent hyperglycemia. Once the patient's sugars are well controlled, they can be switched to a basal-bolus regimen with subcutaneous insulin, and fingerstick frequency can be reduced to every 4 h.

Patients will require tube feeds until they are able to tolerate an oral diet, and pancreatic enzyme supplementation will be required with every feed. In our experience, patients can often escalate to liquids within a few days and solids within weeks. It is critical they work with a dietician throughout this phase to ensure adequate nutrition and education is provided. Additionally, fat-soluble vitamin supplementation should also be considered, particularly vitamin D, as many patients are deficient prior to TP-IAT. For more detailed information on nutrition management with pancreaticoduodenectomy-induced exocrine insufficiency, see Chap. 12 – "Optimizing Nutrition for the Patient after Pancreaticoduodenectomy: Pancreatic Insufficiency."

Regarding pain management, patients should be weaned from narcotics as soon as possible. In the immediate postoperative period, it is appropriate to use a patient-controlled analgesia system, which can be dose adjusted as needed as the patient switches over to oral medications. Pediatric patients and those with lower preoperative morphine requirements will be easier to de-escalate [10, 11] and may be completely narcotic independent within a few weeks of the operation.

Outcome

Upon hospital discharge, the patient required 60 units insulin glargine nightly with 1–15 units of lispro every four hours. In addition, his narcotic dose was temporarily increased for post-surgical pain, and his pancreatic enzyme dose was escalated to accomodate his tube feeding regimen. At one month post-TP-IAT, he is eating 3 meals per day with excellent appetite, and his jejunal feeding tube is removed.

Three months following his operation, the patient is completely pain-free and requires no narcotics. His only residual symptom is occasional steatorrhea that is manageable with an additional increase in pancreatic enzyme replacement therapy. He has de-escalated his diabetes regimen to 20 units of insulin detemir each night, sliding scale insulin aspart and metformin. He has returned to school and feels a dramatic improvement in his quality of life. He will follow up with his gastroenterology and endocrinology teams at 6, 12, and 24 months post TP-IAT for continued monitoring.

Clinical Pearls/Pitfalls

- TP-IAT can provide excellent pain relief in patients with refractory pancreatitis
- About one-third of patients will become insulin independent following TP-IAT; an additional fraction will have partial islet function that reduces insulin requirements
- An extensive preoperative evaluation is required to qualify patients for TP-IAT

- Islet cell isolation can be completed intraoperatively in equipped facilities, or can be conducted at a remote site
- Postoperative management is complex and necessitates attentive glucose monitoring, pain control, and dietary adjustments

References

1. Sutherland DER, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg. 2012;214(4):409–24.
2. Chinnakotla S, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis. indication, surgical techniques, post operative management and long-term outcomes. Ann Surg. 2014;260(1):56.
3. Davies JM, et al. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: Prepared on behalf of the British Committee for Standards in Haematology by a Working Party of the Haemato-Oncology Task Force. Br J Haematol. 2011;155(3):308–17.
4. Kesseli SJ, Smith KA, Gardner TB. Total pancreatectomy with islet autologous transplantation: the cure for chronic pancreatitis? Clin Transl Gastroenterol. 2015;6(1):e73.
5. Wilhelm JJ, et al. Proposed thresholds for pancreatic tissue volume for safe intraportal islet autotransplantation after total pancreatectomy. Am J Transplant. 2013;13(12):3183–91.
6. Merani S, et al. Optimal implantation site for pancreatic islet transplantation. Br J Surg. 2008;95(12):1449–61.
7. Baradi H, et al. Postoperative jejunal feeding and outcome of pancreaticoduodenectomy. J Gastrointest Surg. 2004;8(4):428–33.
8. Padussis JC, et al. Feeding jejunostomy during Whipple is associated with increased morbidity. J Surg Res. 2014;187(2):361–6.
9. Merino JF, et al. Optimal insulin treatment in syngeneic islet transplantation. Cell Transplant. 1999;9(1):11–8.
10. Bellin MD, et al. Outcome after pancreatectomy and islet autotransplantation in a pediatric population. J Pediatr Gastroenterol Nutr. 2008;47(1):37–44.
11. Ahmad SA, et al. Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. J Am Coll Surg. 2005;201(5):680–7.

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T.B. Gardner, K.D. Smith (eds.), *Pancreatology*,
DOI 10.1007/978-3-319-53091-8,