First-line treatment for dumping syndrome is dietary, with smaller, more frequent meals and ingestion of liquids after meals. Decreasing carbohydrate intake, especially simple carbohydrates, and increasing protein and fiber intake may also alleviate symptoms.

Acarbose, an α-glycosidase hydrolase inhibitor that interferes with digestion of polysaccharides to monosaccharides, can be used for late symptoms of dumping syndrome. Other pharmacologic therapies include anticholinergics to slow gastric emptying and antispasmodics. Severe cases of dumping rarely require octreotide. If a trial of subcutaneous injections is effective, monthly intramuscular injections of long-acting octreotide can be used.

KEY POINTS

- Patients who undergo partial gastrectomy for malignancy require lifelong surveillance for cancer recurrence; patients who have undergone partial gastrectomy for benign disease also have an increased risk for gastric cancer.
- Dumping syndrome results from rapid gastric emptying after gastric surgery; first-line treatment is smaller, more frequent meals with liquids taken following meals.

Disorders of the Pancreas

Acute Pancreatitis

Acute pancreatitis is an inflammatory process involving the pancreas and extrapancreatic organs and is the most common gastrointestinal cause of hospitalization in the United States. Biliary disease, including gallstones, biliary sludge, and biliary crystals (microlithiasis), is the most common cause of acute pancreatitis (**Table 14**). Premature activation of digestive enzymes and release of cytokines cause autodigestion of the pancreas and inflammation, which may involve surrounding tissues and distant organs.

Acute pancreatitis is classified as mild, moderately severe, or severe. Mild acute pancreatitis does not involve organ failure or other complications, usually resolves within 1 week, and has a low mortality rate. Twenty percent of patients with acute pancreatitis develop moderately severe or severe disease. Moderately severe acute pancreatitis involves local or systemic complications, such as necrosis or organ failure lasting less than 48 hours. Severe acute pancreatitis involves systemic inflammatory response syndrome (SIRS), persistent organ failure (usually kidney or respiratory failure), duration longer than 48 hours, and one or more local complications. The mortality rate is as high as 50%.

Clinical Presentation and Diagnosis

The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute-onset abdominal pain characteristic of pancreatitis (severe, persistent for hours to days, and epigastric in location, often radiating to the back); (2) serum lipase or amylase levels elevated at least three times the upper limit of normal; and (3) characteristic imaging findings (**Figure 9**). High fever and leukocytosis are part of the cytokine cascade and do not necessarily indicate infection.

Patients with acute pancreatitis should undergo transabdominal ultrasonography to assess for gallstones and biliary duct dilation. Transabdominal ultrasonography is preferred

TABLE 14. Causes of Acute Pancreatitis

Common
Biliary disease
Gallstones
Biliary sludge
Microlithiasis (1- to 2-mm stones that are not detected by imaging studies)
Alcohol use
Postendoscopic retrograde cholangiopancreatography
Occasional
Medications[a]
Furosemide
Didanosine
Asparaginase
Mesalamine
Thiazides
6-Mercaptopurine/azathioprine
Sulfasalazine
Simvastatin
Hypertriglyceridemia
Hypercalcemia
Type V choledochocele
Rare
Autoimmune
Infectious
Viral (mumps, coxsackie B virus, cytomegalovirus, hepatitis B virus, varicella-zoster virus, herpes simplex virus, HIV)
Parasitic (*Toxoplasma* species, *Ascaris lumbricoides*, *Cryptosporidium* species)
Bacterial (*Legionella*, *Leptospira*, *Mycoplasma*, and *Salmonella* species)
Fungal (*Aspergillus* species)
Ischemia
Trauma
Neoplasia
Celiac disease
Genetic (only if attacks recur)

[a]Multiple medications have been linked to acute pancreatitis. A partial list of other suspect medications includes metronidazole, pentamidine, stibogluconate, tetracycline, sulfasalazine, L-asparaginase, valproic acid, sulindac, salicylates, estrogen, and calcium.

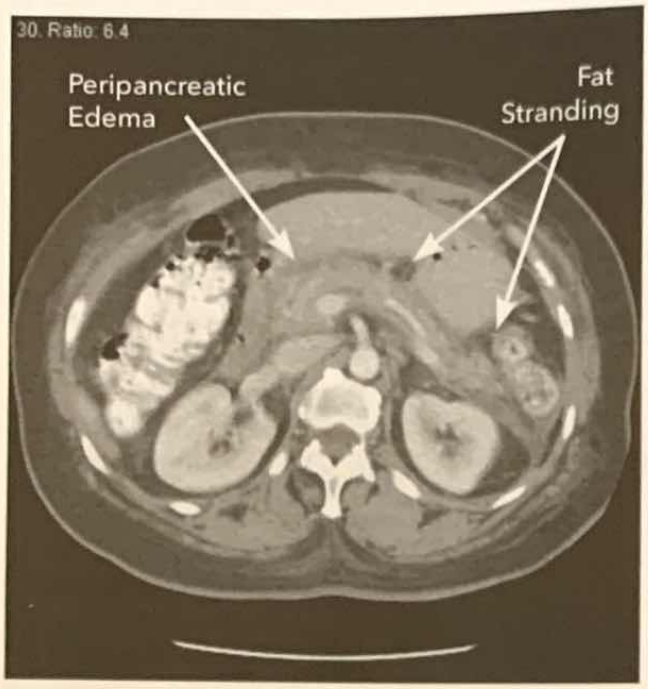

FIGURE 9. CT scan showing acute pancreatitis with peripancreatic fat stranding and inflammation. The hazy appearance of the mesenteric fat surrounding the pancreas in this image is called fat stranding, and the blurring of the margins of the pancreas is consistent with peripancreatic edema, features seen with inflammatory changes of acute pancreatitis.

over CT because it has a higher sensitivity for detecting gallstones, avoids the risks of intravenous contrast material, and is more cost-effective. Magnetic resonance cholangiopancreatography may be considered in patients without abnormal findings on ultrasonography when concern remains for concomitant biliary disease. Although less useful for assessing the biliary system, CT may be indicated if the diagnosis is in question or clinical symptoms are not improved within the first 48 hours (especially because abdominal air can limit ultrasonographic visualization of the pancreas).

A serum alanine aminotransferase level greater than 150 IU/L suggests gallstone pancreatitis. Hyperbilirubinemia should raise suspicion of biliary obstruction and/or cholangitis. Serum amylase and lipase levels may be elevated in conditions other than acute pancreatitis, such as kidney disease, acute appendicitis, cholecystitis, intestinal obstruction or ischemia, peptic ulcer, or gynecologic disorders. Enzyme levels may be falsely low or normal in patients with hypertriglyceridemia-induced pancreatitis because of lipemic-serum interference with laboratory assays. Triglyceride levels should be measured in patients without a biliary cause of acute pancreatitis; a triglyceride level exceeding 1000 mg/dL (11.3 mmol/L) can be considered the cause of the acute pancreatitis.

Prognostic Criteria

Risk factors for severe disease include age older than 55 years, medical comorbidities, BMI greater than 30, presence of SIRS, signs of hypovolemia on presentation (e.g., serum blood urea nitrogen level >20 mg/dL [7.1 mmol/L] and rising, hematocrit >44%, or elevated serum creatinine level), presence of pleural effusions and/or infiltrates, and altered mental status. A systematic review of 18 multiple-factor scoring systems, including the Ranson criteria and the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, for predicting outcome in acute pancreatitis found these systems to have limited clinical value and accuracy. Scoring systems identify severe disease only as it develops, without enough lead time for intervention, and they are too cumbersome for routine use. Elevated hematocrit, elevated blood urea nitrogen levels, and the presence of SIRS are as accurate as complex scoring systems in predicting outcome, and they are easier to use.

Management

Mainstays of initial management include fluid resuscitation, pain management, and antiemetics.

Early and aggressive fluid resuscitation (250-500 mL/h of intravenous normal saline or lactated Ringer solution) should be given to patients with acute pancreatitis on presentation and is most beneficial in the first 12 to 24 hours. More rapid fluid resuscitation (boluses) may be needed in patients with severe volume depletion in order to maintain organ perfusion. Patients with organ failure or SIRS should be admitted to an ICU or intermediary care setting, with fluid requirements reassessed every 6 hours for the first 24 to 48 hours.

Routine use of antibiotics is not warranted in acute pancreatitis unless there is evidence of extrapancreatic infection, such as ascending cholangitis, bacteremia, urinary tract infection, or pneumonia. Use of prophylactic antibiotics in patients with sterile pancreatic necrosis to prevent infected necrosis is not recommended.

In mild acute pancreatitis, oral feedings can be started as soon as nausea and vomiting are controlled and clinical symptoms improve. Enteral feeding should begin within 72 hours if oral feeding is not tolerated; it is usually required in patients with moderately severe or severe acute pancreatitis. Feeding with a nasojejunal tube has traditionally been preferred, but data suggest that nasogastric feedings are probably as effective and are easier to administer. Enteral feeding promotes a healthy gut-mucosal barrier and may prevent translocation of bacteria into inflamed tissues.

If a biliary cause of acute pancreatitis is suspected, serial liver chemistry tests and clinical symptoms can show whether the biliary obstruction is ongoing or resolving. Endoscopic retrograde cholangiopancreatography (ERCP) is not indicated in patients with gallstone pancreatitis unless there is persistent biochemical evidence of biliary obstruction or choledocholithiasis is seen on imaging. Patients with cholangitis should undergo ERCP within 24 hours of admission. Magnetic resonance cholangiopancreatography can be useful when there is persistent elevation of liver chemistries without overt cholangitis or biliary obstruction. Patients with uncomplicated gallstone pancreatitis should be considered for cholecystectomy before discharge.

There is no value in rechecking serum amylase and lipase levels after the diagnosis is established.

Complications

There are two overlapping phases of acute pancreatitis with two peaks in mortality. The early phase is the first week of the disease. In this phase, the body is responding to local pancreatic injury and the cytokine cascade; SIRS and organ failure, especially kidney and respiratory failure, are possible, as is profound hypocalcemia. The late phase occurs after the first week and may persist for weeks to months in patients with moderately severe or severe acute pancreatitis. Significant risk for infection in peripancreatic fluid collections and necrotic tissue occurs in the late phase.

Proper classification of fluid collections in acute pancreatitis is important to guide management. In 2012, an international consensus group updated the Atlanta classification and definitions of acute pancreatitis and its complications to promote consistency in diagnosis and management. The group defined four types of fluid collections:

1. Acute peripancreatic fluid collections occur in edematous interstitial pancreatitis (no necrosis) within the first 4 weeks, are thought to result from rupture of main or side-branch ducts because of inflammation, are sterile, and usually resolve spontaneously.
2. Pancreatic pseudocysts are acute peripancreatic fluid collections that have persisted for longer than 4 weeks, have developed a well-defined wall, and contain no solid debris (necrosis).
3. Acute necrotic collections (**Figure 10**) are areas of necrosis in the pancreatic parenchyma and/or peripancreatic tissues within the first 4 weeks of acute pancreatitis.

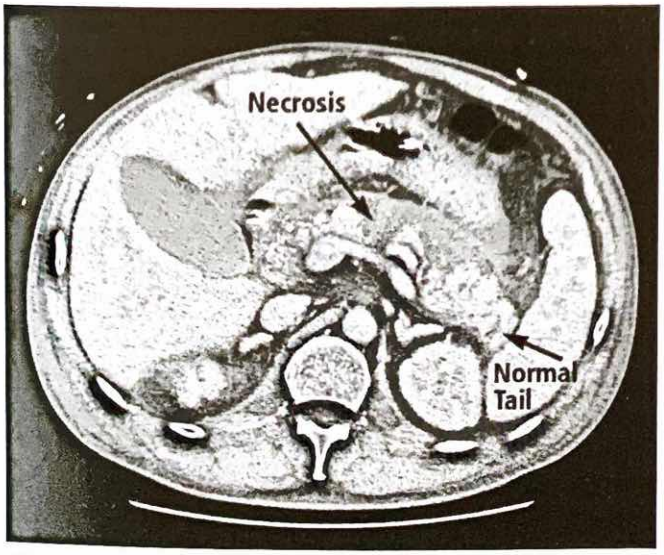

FIGURE 10. CT scan showing acute pancreatitis with hypoperfusion of the body of the pancreas, as indicated by lack of enhancement following intravenous contrast infusion (necrosis) and normal perfusion of the pancreatic tail.

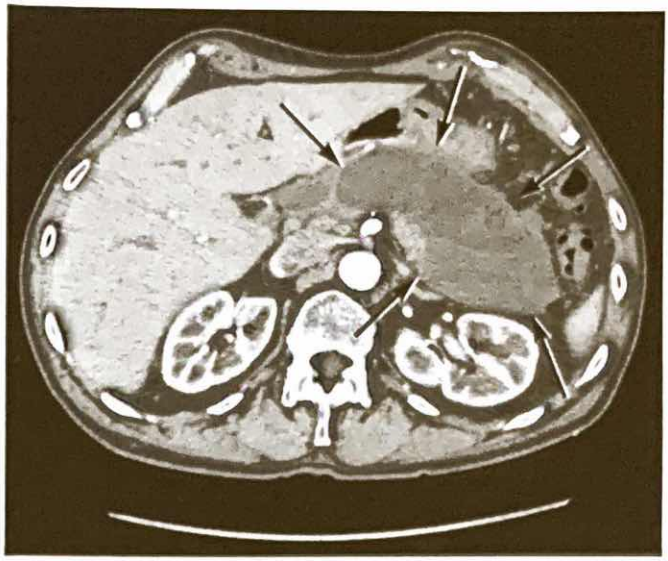

FIGURE 11. CT scan showing maturation and liquefaction of pancreas necrosis of nearly the entire pancreas over 4 weeks' duration with a well-defined rim or wall (*arrows*), known as walled-off necrosis.

4. Walled-off necrosis (**Figure 11**) occurs after 4 weeks, when the body liquefies the necrosis and contains it within a well-defined wall.

Contrast-enhanced CT may not be able to distinguish solid from liquid content in fluid collections; therefore, necrotic collections are frequently misdiagnosed as pancreatic pseudocysts. Pancreatic pseudocysts do not require drainage unless they cause significant symptoms or are infected, regardless of size.

Because they contain only fluid, pseudocysts are easily drained under endoscopic or radiographic guidance. Walled-off necrosis is not as amenable to percutaneous or endoscopic drainage because of solid necrotic debris within the cavity and may require surgical debridement.

The management of suspected infected necrosis includes initiation of antibiotics (e.g., imipenem-cilastatin, meropenem, or ciprofloxacin plus metronidazole), with consideration of fine-needle aspiration with Gram stain and culture under CT guidance. Drainage procedures or debridement should be delayed for at least 4 weeks if possible to allow encapsulation of the necrosis with a fibrous wall.

KEY POINTS

- Biliary disease (gallstones, biliary sludge, or microlithiasis) is the most common cause of acute pancreatitis.
- Diagnosis of acute pancreatitis requires two of three criteria: (1) acute-onset upper abdominal pain, (2) serum lipase or amylase levels elevated at least three times the upper limit of normal, and (3) characteristic findings on imaging.
- Patients with acute pancreatitis should undergo transabdominal ultrasonography rather than CT for evaluation of biliary disease. HVC

(Continued)

KEY POINTS *(continued)*

- Early and aggressive fluid resuscitation should be initiated in patients with acute pancreatitis.
- In mild acute pancreatitis, oral feedings can be started as soon as nausea and vomiting are controlled and clinical symptoms are alleviated; enteral feeding should begin within 72 hours if oral feeding is not tolerated.
- Pancreatic pseudocysts do not require drainage unless they cause significant symptoms or are infected, regardless of size.

Chronic Pancreatitis

Chronic pancreatitis is thought to develop when the inflammatory response to acute pancreatitis persists and ongoing inflammation activates stellate cells, resulting in a fibroinflammatory response. This causes distorted tissue architecture, loss of normal parenchyma, activation of pancreatic nociceptors, and loss of acinar and islet cell function. Genetic variants affecting inflammatory response, enzyme activation, and tissue repair are thought to play important roles in the pathogenesis of chronic pancreatitis. Many genes have been identified as disease modifiers, but the gene-environment interaction is not fully understood.

Alcohol use has long been described as a risk factor for chronic pancreatitis, but less than 3% of heavy alcohol users develop pancreatic disease. Patients who consume more than five drinks per day (or 35 drinks per week) seem to be more susceptible to chronic pancreatitis. In the largest study of patients with chronic pancreatitis in North America, only 46% had a history of significant alcohol use. The higher prevalence of alcohol-associated pancreatitis among men could be partially explained by an X chromosome–linked genetic variant, the *CLDN2* gene. Tobacco is considered an independent risk factor. **Table 15** lists causes of chronic pancreatitis.

TABLE 15. Causes of Chronic Pancreatitis

Toxic or metabolic
Alcohol, tobacco, hypercalcemia, hypertriglyceridemia, chronic kidney disease
Genetic
Mutations or polymorphisms of the *CFTR*, *PRSSI*, *SPINKI*, *CTRC*, *CASR*, *CLDN2* genes
Recurrent and severe acute pancreatitis
Vascular disease/ischemia
Obstructive
Pancreatic tumor, intraductal papillary mucinous neoplasm
Posttraumatic (pancreatic duct stricture)
Autoimmune (type 1 and type 2)
Idiopathic

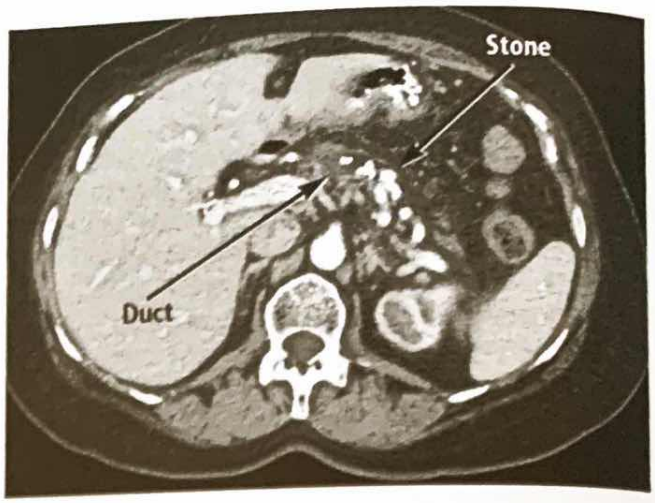

FIGURE 12. CT scan showing chronic calcific pancreatitis with multiple stones in the main duct and side branches of the pancreas.

Clinical Presentation and Diagnosis

Abdominal pain is the most common presenting symptom of chronic pancreatitis (seen in 85% of patients), but some patients have no pain. Pain patterns can vary from constant daily pain to intermittent attacks of severe pain. Pancreatic enzyme levels may not increase during attacks of pain because of fibrosis and atrophy of acinar cells and decreased enzyme production. Constant daily pain in chronic pancreatitis significantly reduces quality of life, with increased use of health care resources and disability benefits and time away from employment. Exocrine or endocrine insufficiency occurs in some patients as a result of significant tissue destruction.

Diagnosis of chronic pancreatitis remains challenging because hallmark anatomic features, such as pancreatic calcifications (**Figure 12**), occur in only 25% of patients, and other features of atrophy or duct dilation can occur normally with aging or other disease processes. Imaging with CT or MRI is the initial test of choice. In the setting of high clinical suspicion and negative findings on imaging, endoscopic ultrasonography and secretin-enhanced magnetic resonance cholangiopancreatography may be useful as second- and third-line tests; pancreatic biopsy may rarely be necessary. ERCP is no longer used as a diagnostic tool for chronic pancreatitis. Genetic testing for cystic fibrosis and familial pancreatitis should be considered in younger patients. Pancreatic exocrine function may be assessed with fecal elastase testing, which has largely replaced fecal fat testing.

Management

Management focuses on treating symptoms. No effective treatment exists to reverse or halt disease progression. Patients should be counseled to avoid alcohol and tobacco to lessen attacks of inflammation and pain. Intermittent attacks of severe acute pain are treated as acute pancreatitis. Possible complications of chronic pancreatitis, including pseudocyst, pancreatic duct stones causing upstream obstruction, and

malignancy, should be evaluated with imaging (e.g., pancreatic-protocol CT) when a patient's symptom pattern changes. Endoscopic techniques are first-line therapy for relief of ductal obstruction. Constant daily pain is more challenging to manage; treatment frequently involves medications such as tramadol, serotonin norepinephrine reuptake inhibitors, gabapentinoids, and opioids. Long-term use of opioids should be avoided because of hyperesthesia and development of tolerance or addiction. Pancreatic enzymes are used to treat steatorrhea but do not effectively treat pain or prevent attacks of pancreatitis. Two large randomized trials of antioxidants to treat chronic pancreatitis pain showed conflicting results; guidelines suggest that antioxidants be considered, although it is unclear which antioxidants and doses are appropriate. Nerve blocks and neurolysis procedures are also recommended, although the response rate is low, and pain relief, if achieved, lasts only a few weeks.

Surgery offers the best long-term results for chronic refractory pain management and, depending on anatomy and cause, may include lateral pancreaticojejunostomy, duodenal-preserving pancreatic head resection, pancreaticoduodenectomy, distal pancreatectomy, or even total pancreatectomy with or without auto-islet-cell transplantation. These procedures improve outcomes in patients at high-volume pancreas referral centers. Pancreatic endocrine insufficiency may require specialty referral for labile diabetes management.

KEY POINTS

- Abdominal pain, which may occur as intermittent attacks or as ongoing daily pain, is the most common symptom of chronic pancreatitis.
- HVC Pancreatic biopsy and endoscopic retrograde cholangiopancreatography are not indicated in the diagnosis of chronic pancreatitis.
- Symptomatic management is the cornerstone of treatment for chronic pancreatitis, including in patients with refractory pain.
- Patients with chronic pancreatitis should be counseled to avoid alcohol and tobacco use.

Autoimmune Pancreatitis and IgG4 Disease

Autoimmune pancreatitis (AIP) is a frequent manifestation of IgG4-related disease. Other organs that can be affected include the lacrimal and salivary glands, central nervous system, kidneys, thyroid gland, lungs, biliary tract and liver, prostate gland, retroperitoneum, and lymph nodes. Storiform fibrosis and obliterative phlebitis are seen in the pancreas and biliary tract. The most common pancreatic manifestation of IgG4-related disease is type 1 AIP, with abundant infiltration of IgG4-positive plasma cells and lymphocytes. Type 2 disease is discussed in Clinical Presentation and Diagnosis. The 2011 International Consensus of Diagnostic Criteria for Autoimmune Pancreatitis endorsed the concept of type 1 and type 2 disease, but there is some debate over whether type 2 should be considered an IgG4-related disease.

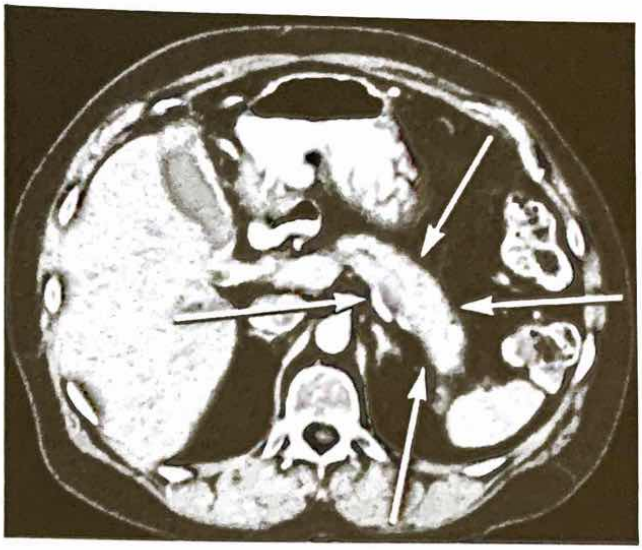

FIGURE 13. CT scan showing the homogeneous, hypodense "sausage-shaped" swelling (*arrows*) seen in autoimmune pancreatitis. The pancreatic duct is not dilated.

For more information on IgG4-related disease, see MKSAP 19 Rheumatology.

Clinical Presentation and Diagnosis

Patients with both types of AIP may present with abdominal pain or obstructive jaundice with or without a mass. In patients presenting with obstructive jaundice or with a mass, pancreatic malignancy must be considered. Many patients with malignancy have a dilated upstream main pancreatic duct. In contrast, patients with AIP may have a narrowed main pancreatic duct or parenchymal swelling ("sausage-shaped" pancreas [**Figure 13**]). Endoscopic ultrasonography and biopsy may be required to differentiate AIP and pancreatic neoplasm. Ten percent of patients with type 1 AIP may develop chronic pancreatitis or pancreatic stone formation.

Patients with type 1 AIP have elevated levels of IgG4-positive cells in pancreatic tissue (>10 IgG4-positive cells/hpf), and 60% to 80% of patients have associated sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Fulfillment of one or more of the HISORt criteria (diagnostic Histology, suggestive Imaging, Serology with elevated serum IgG4, Other organ involvement, or Response to therapy with glucocorticoids) can be helpful in the diagnosis of type 1 AIP.

Type 2 AIP has no or few IgG4-positive cells but is characterized by idiopathic duct-centric neutrophil infiltration, known as a granulocytic epithelial lesion. Type 2 AIP is a pancreas-specific disease occasionally associated with inflammatory bowel disease.

Treatment

Glucocorticoids are effective treatment for types 1 and 2 AIP, starting with oral prednisolone at 0.6 to 1.0 mg/kg/d and

tapered over 2 to 3 months. Response is determined by symptom relief and imaging features. Failure of clinical symptoms to respond to glucocorticoids suggests an incorrect diagnosis, and other causes should be investigated. Up to 60% of patients may relapse. Glucocorticoids or immunomodulators, such as 6-mercaptopurine, azathioprine, mycophenolate, or rituximab, may be re-adminstered to treat recurrent AIP.

KEY POINTS

- Diagnosis of autoimmune pancreatitis requires the presence of a narrowed main pancreatic duct and parenchymal swelling ("sausage-shaped" pancreas) on imaging and disease response to glucocorticoids.
- Type 1 autoimmune pancreatitis is characterized by elevated numbers of IgG4-positive cells in pancreatic tissue; most patients also have a significant elevation of IgG4 in serum.
- Patients with type 2 autoimmune pancreatitis have normal IgG4-positive cell counts.
- Types 1 and 2 autoimmune pancreatitis are treated with glucocorticoids, with a relapse rate of up to 60%.

Pancreatic Adenocarcinoma

Pancreatic ductal adenocarcinoma has a poor prognosis and increasing incidence. In 2019, there were approximately 57,000 cases diagnosed in the United States and 46,000 deaths. It is predicted to become the second leading cause of cancer-related death in the United States over the next decade, with an overall 5-year survival rate of 9%.

Epidemiology and Risk Factors

Risk factors for pancreatic cancer include age older than 50 years, smoking history, obesity, chronic pancreatitis, and mucinous cystic lesions of the pancreas. Inherited conditions associated with pancreatic cancer include Peutz-Jeghers syndrome, *BRCA2* germline mutations, hereditary pancreatitis, familial atypical multiple-mole melanoma, Lynch syndrome, and familial pancreatic cancer with at least two affected first-degree relatives.

Clinicians should not screen average-risk individuals for pancreatic cancer. The American Gastroenterological Association and the International Cancer of the Pancreas Screening Consortium recommend that clinicians screen select high-risk patients for pancreatic cancer, including those with a genetic predisposition to disease. If possible, screening should be performed at a center experienced in the diagnosis and treatment of pancreatic adenocarcinoma.

Clinical Presentation

Symptoms of pancreatic adenocarcinoma include abdominal pain, back pain, weight loss, and jaundice (if the lesion obstructs the common bile duct). Pancreatic cancer is highly associated with diabetes mellitus, and two thirds of patients develop new-onset diabetes mellitus in the 36 months surrounding the diagnosis. Venous thromboembolic events and depression occur at higher rates in patients with pancreatic adenocarcinoma than in patients with other malignancies.

Diagnosis

Pancreas-protocol CT uses multiphasic arterial and venous phases with thin cuts (3 mm) through the abdomen to view the primary tumor's relationship to mesenteric vasculature and to detect metastatic lesions. Some studies suggest that pancreas-protocol MRI may be superior to CT for pancreatic disease. Histopathologic confirmation of pancreatic adenocarcinoma is increasingly recommended before initiation of therapy. In patients with potentially resectable disease, endoscopic ultrasonography-guided fine-needle aspiration biopsy is recommended for histologic confirmation of cancer. It is preferable to CT-guided biopsy because of its higher diagnostic yield, safety, and lower risk for peritoneal seeding. Patients are considered for primary surgical resection if they have no involvement of mesenteric vasculature or metastatic disease and are healthy enough for major intra-abdominal surgery.

For staging and treatment of pancreatic cancer, see MKSAP 19 Oncology.

KEY POINTS

- Diagnosis of pancreatic cancer is suggested by abdominal pain, weight loss, jaundice, and new-onset diabetes mellitus; pancreas-protocol CT or MRI helps support the diagnosis and delineates the extent of disease.
- In patients with potentially resectable disease, endoscopic ultrasonography-guided fine-needle aspiration of the pancreas is recommended for histologic confirmation of cancer.

Cystic Lesions of the Pancreas

Pancreatic cysts are found incidentally in 15% of patients undergoing abdominal imaging. The detection of a cystic lesion in the pancreas causes anxiety in patients and clinicians and is a growing driver of health care use in the United States.

Cystic neoplasms of the pancreas are subcategorized as mucin-producing and nonmucin-producing cysts (**Figure 14**). Mucin-producing cysts, including intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, are thought to have malignant potential, but many never become malignant. Intraductal papillary mucinous neoplasms are the most common cystic lesions of the pancreas. Most intraductal papillary mucinous neoplasms arise from a side branch of the pancreatic duct and have a low rate of malignant transformation. In contrast, the rate of malignant transformation is as high as 65% in intraductal papillary mucinous neoplasms involving the main pancreatic duct (**Figure 15**). Other worrisome features are presence of symptoms (jaundice, pancreatitis), cyst size greater than 3 cm, dilated main pancreatic duct, and a solid cyst component.