Chronic Pancreatitis

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Introduction

Chronic pancreatitis is characterized by chronic inflammation and fibrosis of the pancreas resulting in impaired exocrine and endocrine function [1]. In true acute pancreatitis, there is restitution of the gland to structural and functional normalcy after an acute attack, characterized by acute abdominal pain, elevated serum amylase/lipase, and morphological changes on imaging. In chronic pancreatitis, patients often experience attacks of clinical acute pancreatitis, but in contrast to true acute pancreatitis there is progressive structural and functional damage to the pancreas despite clinical recovery from the attacks. Despite the differences in the two entities, an emerging body of literature suggests that some patients with (recurrent) acute pancreatitis may progress to chronic pancreatitis [1].

Epidemiology

In the United States, pancreatitis was listed as the "first-listed diagnosis" in 72,000 hospital discharges and 101,000 ambulatory visits for patients aged ≥65 years in 2004 [2]. A survey in Japan revealed the prevalence of chronic pancreatitis in men between 65 and 69 years of age to be 115 per 100,000 population and in women aged 75–79 years to be 39.6 per 100,000 population [3]. A prospective survey of gastroenterologists in France yielded a crude prevalence of 26 per 100,000 and estimated that about 20% of chronic pancreatitis cases occurred in the over 65 year age group [4].

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Effects of Aging on the Pancreas

Studies of changes on exocrine pancreatic function with aging yield conflicting data. Early studies showed a 10–30% reduction in the volume, bicarbonate, and lipase in pancreatic juice in elderly patients [5]. In contrast, there was no difference in secretin stimulated pancreatic secretion between 25 older subjects and 30 young controls [6]. Experience with secretin stimulation tests over 10 years did not show a decrease in bicarbonate secretion with age [5]. These contradictory data may be due to differences in methodology and inadvertent inclusion of asymptomatic pancreatic disease. Regardless, even if there was some age related decline (10–30%), this would not be clinically relevant, since >90% of the pancreas has to be damaged to cause clinically evident exocrine insufficiency [7].

In contrast to the effects of age on function, marked changes in pancreatic structure occur with aging. Autopsy series reveal duct proliferation, lobular degeneration, and fatty infiltration [5, 8, 9]. Pancreatic lithiasis ranges from being absent in those <70 years to being present in 16% of patients >90 years [10]. Pancreatic lithiasis was found in the peripheral ducts upstream from sites of squamous metaplasia, was asymptomatic and was not associated with alcoholism or hypercalcemia [10]. Extensive parenchymal atrophy and fibrosis was also seen in areas upstream from the stones. Postmortem pancreatography performed by physicians trained in endoscopic retrograde cholangiopancreatography (ERCP) found ductal changes similar to those seen in chronic pancreatitis in 81% of older adults [11, 12]. However, histopathology in the same cases confirmed the findings to be age-related and not due to chronic pancreatitis [11]. The suggested ERCP criteria for the diagnosis of chronic pancreatitis in the elderly are summarized in Table 44.1 [12, 13].

Age-related pancreatic changes are also seen on endoscopic ultrasonography (EUS). In a prospective study of 120 patients without pancreatic disease, 39% patients >60 years had at least one EUS abnormality of chronic pancreatitis [14]. In this study, the presence of >3 EUS abnormalities,

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Table 44.1 ERCP criteria for diagnosis of chronic pancreatitis in the elderly (Adapted from Gloor et al. [12], Jones et al. [13])

Ductal obstruction and stricture
Gross irregularity of the main pancreatic duct
Presence of large cavities (>5 mm) (due to prestenotic ductal dilation)

ductal or parenchymal stones, ductal narrowing or dilation were more likely to represent disease than age-related changes [14]. Thus, caution should be exercised when interpreting ERCP and EUS findings in the geriatric patient.

Risk Factors

Idiopathic Chronic Pancreatitis

Most chronic pancreatitis with onset in the old are due to "late-onset" idiopathic disease, originally described as "senile" chronic pancreatitis by Amman et al. and characterized by an age of onset of 56 years, absence of pain, and early development of structural (diffuse calcifications) and functional (exocrine and endocrine) abnormalities [15, 16]. This is in contrast to "early-onset" idiopathic disease with a mean age of onset of 20 years, presence of pain and longer delay to the development of pancreatic abnormalities [16, 17].

Obstructive Pancreatitis

Obstruction of the main pancreatic duct (e.g., by an ampullary malignancy or cancer in the pancreatic head) can be an important cause in the elderly patient with new-onset chronic pancreatitis [12, 18]. This form of chronic pancreatitis differs from other varieties in the absence of calcifications and higher prevalence of a dilated pancreatic duct [18].

Alcoholic Chronic Pancreatitis

In the general population, alcohol is the most common cause of chronic pancreatitis, accounting for 70–80% cases; however in patients with onset of pancreatitis after the age of 65, alcohol is an exceedingly uncommon cause [19]. The risk increases with increasing dose (>4 drinks/day) and duration (>10 years) of alcohol consumption [20]. While alcohol appears to play an important role in the development of chronic pancreatitis, only 5–15% of alcoholics develop the disease, suggesting a role for cofactors such as genetics, tobacco, etc. [20].

Tobacco

While smoking is an independent risk factor for chronic pancreatitis, the damage to the pancreas is compounded by ongoing alcohol use [21].

Recurrent Acute Pancreatitis

Approximately 1 out of every 5 patients with acute alcoholic pancreatitis progresses to chronic pancreatitis [22].

Other Causes

- *Hereditary pancreatitis* is an uncommon cause of chronic pancreatitis. While mutations in the cationic trypsinogen gene (PRSS1) are most commonly associated with chronic pancreatitis, mutated cystic fibrosis gene (CFTR) and trypsin inhibitor (SPINK1) genes are being increasingly identified in patients with idiopathic chronic pancreatitis [23, 24].
- *Autoimmune pancreatitis (AIP)*: This entity is discussed in a separate section.
- *Tropical pancreatitis*: Although the life expectancy of patients with tropical pancreatitis has considerably improved, it is not yet a geriatric problem. The entity is common in southern India and is characterized by onset at young age, severe malnutrition, diabetes mellitus, and pancreatic calculi.

In summary, the etiology of chronic pancreatitis may be attributed to a complex interplay of environmental and genetic factors. The former include alcohol, tobacco and occupational chemicals, while the genetic factors include mutations in trypsin-controlling or cystic fibrosis genes [25].

Clinical Presentation

Abdominal pain, an uncommon symptom in late-onset idiopathic chronic pancreatitis, is often a major complaint in alcoholic chronic pancreatitis [12, 16]. The typical pain is epigastric, postprandial, radiates to the back, and is relieved by sitting up or leaning forward.

Pancreatic exocrine insufficiency is often the presenting symptom in patients with late-onset idiopathic chronic pancreatitis [16]. While protein and carbohydrate malabsorption might occur in advanced pancreatic insufficiency, they are generally less pronounced than fat malabsorption due to intact salivary amylase and brush border peptidases in most patients. Most patients with exocrine insufficiency present with greasy, foul-smelling stools (steatorrhea). Patients might also present with weight loss, malnutrition, fat-soluble vitamin deficiencies (Vitamin A, D, E, and K) and vitamin B12 deficiency (due to noncleavage of R-factor from vitamin B12, dependent on pancreatic function).

Endocrine pancreatic insufficiency ranges from mild to severe insulin-requiring diabetes.

Diagnosis

No single diagnostic test is adequately sensitive or specific for chronic pancreatitis in all patients. Age-related structural changes in the older adult may make the diagnosis even more difficult. A suggested diagnostic algorithm for chronic pancreatitis is outlined in Fig. 44.1.

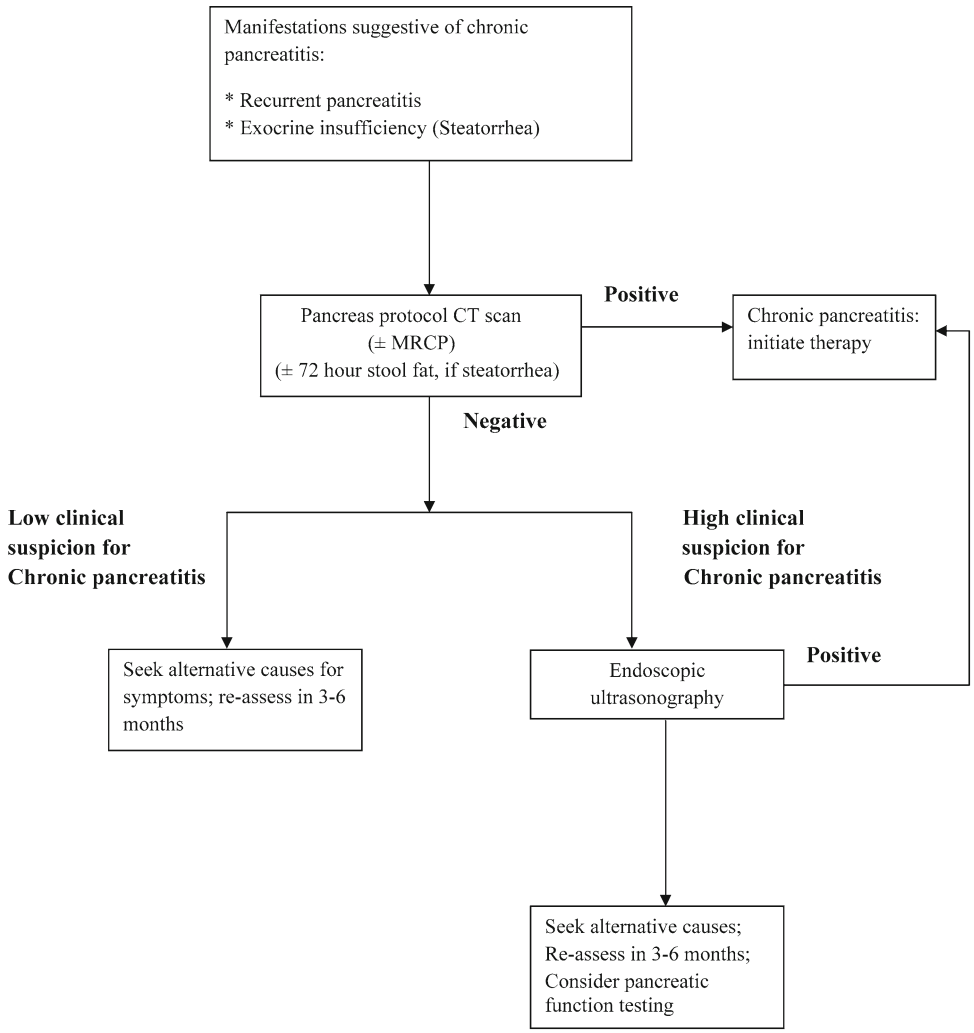

Fig. 44.1 Diagnostic algorithm for suspected chronic pancreatitis (Adapted from Etemad et al. [24])

Tests of function

- *Amylase and lipase levels*: Amylase and lipase levels are generally normal (due to fibrosis) and are not useful in the diagnosis of chronic pancreatitis.
- *Stool fat quantitation*: A 72-h fecal fat quantitation is useful in patients with steatorrhea. Patients with pancreatic insufficiency typically excrete >10–14 g of fat. Since exocrine pancreatic insufficiency develops only when <10% secretory capacity remains, this test is not useful in the diagnosis of early disease [7]. Further, the test is cumbersome in the elderly.
- *Stool elastase and chymotrypsin*: These tests are a measure of the secretion of elastase and chymotrypsin by the pancreas on random stool samples [26]. However, they provide yield only in the presence of steatorrhea, obviating their utility in the diagnosis of early disease [27].
- *Hormonal stimulation tests*: They measure pancreatic secretory capacity by collecting pancreatic fluid following stimulation with a secretagogue (e.g., secretin). Hormonal stimulation tests are considered the most sensitive tests (70–90%) for chronic pancreatitis [28]. While they detect early disease, there is a risk of complications from invasive endoscopic procedures [29].

Tests of structure

- *Plain radiography*: Diffuse calcifications in the pancreatic duct are very specific for chronic pancreatitis and often seen in elderly smokers with late-onset idiopathic disease [30] (Fig. 44.2).
- *Ultrasonography (USG)*: Transabdominal ultrasound has limited utility in evaluation of the pancreas due to interference by bowel gas and body fat [31].
- *Computed tomography (CT)*: CT has the advantage of adequate imaging regardless of body habitus, but carries risk of radiation exposure. However, the higher sensitivity (80–90%) and specificity (85%) for diagnosis of chronic pancreatitis justify its widespread use [32].
- *Magnetic resonance cholangiopancreatography (MRCP)*: MRCP is increasingly becoming the preferred test in the diagnosis of chronic pancreatitis since it can detect ductal

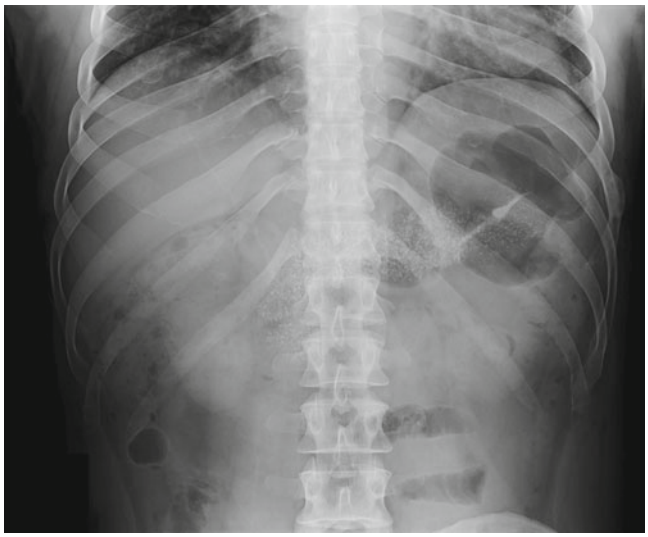

Fig. 44.2 Abdominal plain film in a patient with chronic pancreatitis with diffuse calcifications in the pancreas

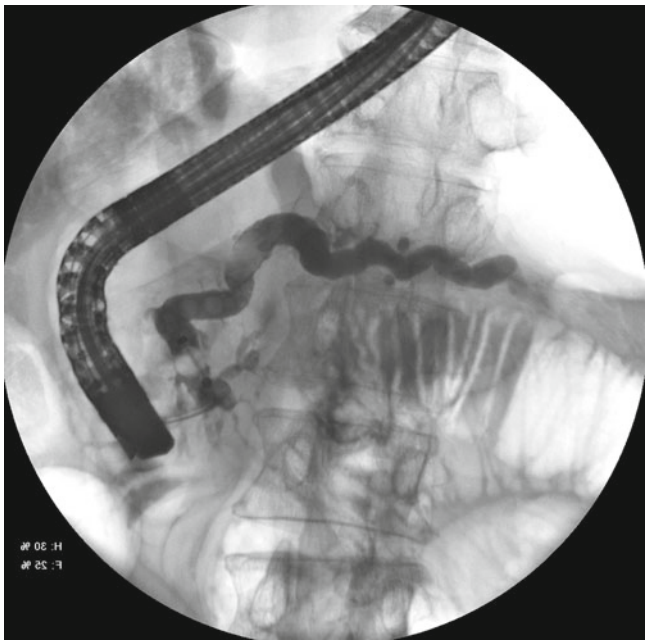

Fig. 44.3 Endoscopic retrograde cholangiopancreatography showing classic changes of chronic pancreatitis in an elderly patient (grossly irregular and dilated main pancreatic duct, dilated side branches, filling defects and stone in the main pancreatic duct)

abnormalities with a similar frequency to ERCP and avoids the risks associated with ERCP [33, 34].

- *Endoscopic retrograde cholangiopancreatography (ERCP)*: ERCP has the highest sensitivity (70–90%) and specificity (80–100%) for the diagnosis of chronic pancreatitis but carries a risk of complications [33]. As discussed earlier, ERCP findings of chronic pancreatitis in the older patient (Fig. 44.3) can be confounded by age-related changes in the normal pancreas [35, 36].
- *Endoscopic ultrasound (EUS)*: EUS criteria for diagnosis of chronic pancreatitis include ductal abnormalities (dilation, irregularity, calcification, etc.) and parenchymal abnormalities (cysts, hyperechoic foci, lobularity, etc.) [36, 37] (Fig. 44.4a, b, c) Besides aging, alcohol, smoking, and acute pancreatitis can all cause EUS abnormalities in the absence of chronic pancreatitis [14, 38]. EUS diagnosis is, therefore, heavily dependent on operator experience.

As chronic pancreatitis is a complex disease, EUS-based criteria for diagnosis have differed widely. A consensus study has established major and minor EUS based criteria for chronic pancreatitis in the "Rosemont Classification" [39]. Further, EUS may be complemented by digital imaging analysis and functional testing; EUS may also be used for celiac plexus blockade and ductal access techniques [40].

Treatment

Therapy for chronic pancreatitis is centered on the management of symptoms.

Abdominal Pain

Lifestyle modifications including abstinence from alcohol and cessation of smoking are associated with a reduction in pain [41]. Supplemental antioxidants (selenium, vitamin A, vitamin C, and vitamin E) have a modest effect on reducing pain [42]. However, most patients require some form of analgesia for pain control. When prescribing analgesics in the elderly, the strategy is to begin with nonnarcotic analgesics followed by low-potency opioids (e.g., tramadol) and finally higher-potency narcotics. The goal is to reduce pain to a manageable level and not complete alleviation. Since chronic pain can lead to depression which in turn exacerbates pain, there is a role for adjunct therapy such as antidepressants. Pancreatic enzymes help reduce pain only in small duct disease, women and those with idiopathic chronic pancreatitis [43]. Patients with worsening abdominal pain require evaluation for complications such as pseudocysts, cancer, stricture, etc.

Since the celiac plexus transmits nociceptive impulses from the pancreas to the spinal cord, blocking these signals (percutaneously, endoscopically, or surgically) can help treat pain in chronic pancreatitis. While EUS guided celiac plexus block (injecting steroids) is safer and more cost-effective than CT guided techniques, the pain relief is temporary. [44] A study of 90 patients showed pain relief in 55% at 4 weeks but by 24 weeks only 10% reported sustained benefit [45]. EUS guided celiac plexus block might be useful in the elderly since pain relief was more evident in those over age 45 years in the previously mentioned study, although its precise role is still evolving [45]. In patients with large duct disease and

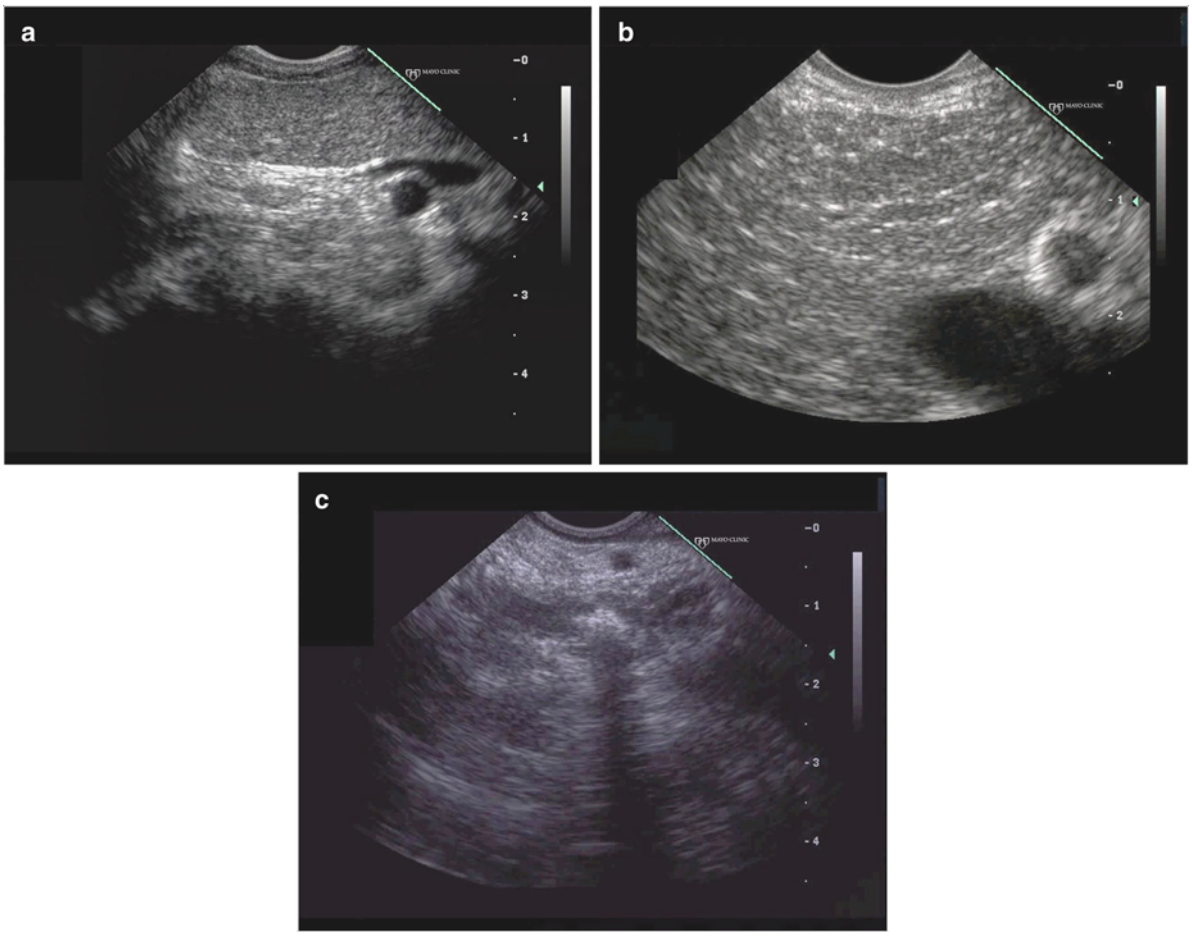

Fig. 44.4 EUS findings in chronic pancreatitis (Courtesy: Dr. Michael J. Levy, Mayo Clinic, Rochester, MN). (**a**) Normal pancreas. (**b**) Hyperechoic foci. (**c**) Dilated main pancreatic duct, intraductal calculus

evidence of pancreatic ductal obstruction (strictures or stones), endoscopic therapy with a pancreatic sphincterotomy with or without pancreatic stenting might be useful [46]. Surgical intervention with ductal drainage or pancreatic resection is reserved for medically refractory disease, suspected malignancy, and complications such as pseudocysts [47].

Steatorrhea

The mainstay of treatment for pancreatic steatorrhea is pancreatic enzyme supplementation. Lipase (30,000–50,000 IU) spread over each meal is generally adequate [28]. A smaller amount is required with snacks. If a non-enteric-coated formulation is selected, concomitant acid suppression (e.g., proton pump inhibitor or H_2 blocker) is necessary. In addition, fat-soluble vitamins should be replaced in patients with steatorrhea. In patients who do not respond, dietary restriction of fat to less than 20 g per day may help relief of steatorrhea, but prevents weight gain. Bacterial overgrowth may complicate steatorrhea and require treatment. Medium chain triglycerides (MCTs), which do not need lipase for absorption, are rarely required to treat pancreatic steatorrhea [28].

Diabetes Mellitus

Diabetes in chronic pancreatitis is usually insulin requiring. In addition, there is increased risk of hypoglycemia due to loss of glucagon secreting alpha cells.

Complications and approach to management are listed in Table 44.2.

Autoimmune Pancreatitis

AIP is a rare autoimmune disorder that is subclassified into two types, based on distinct pathological and clinical profiles [52]. Type 1 or lymphoplasmacytic sclerosing pancreatitis is characterized by infiltration of the pancreas by IgG4 positive plasma cells (Fig. 44.5a, b) and typically affects elderly men. Over 80% of patients with type 1 AIP are males, with >80% over age 50 [52]. Type 1 disease is also associated with a higher relapse rate as well as extrapancreatic involvement. In contrast, type 2 or idiopathic duct centric pancreatitis is characterized by a granulocytic epithelial lesion (GEL) with minimal IgG4 positive cells and affects younger patients

Table 44.2 Complications of chronic pancreatitis [48–51]

Complication	Cause	Presentation	Diagnosis	Treatment
Pseudocyst	Ductal disruption	Abdominal pain Bleeding Bowel/biliary obstruction Ascites (from disruption)	Imaging with USG, CT, MRI, EUS	No treatment, if asymptomatic Drainage, if symptomatic, enlarging or complicated
Biliary/duodenal obstruction	Inflammation or fibrosis in the head leading to compression	Jaundice Nausea, vomiting, abdominal pain	CT MRCP EGD	Surgical bypass or endoscopic stenting
Pancreatic fistulae and ascites	Ductal disruption, pseudocyst rupture	Abdominal pain Ascites	High amylase on paracentesis	TPN, NPO, octreotide Endoscopic stenting Surgery
Splenic vein thrombosis	Contiguous inflammation	Gastrointestinal bleeding from gastric varices	EGD USG with Doppler CT	No treatment if asymptomatic Endoscopic glue for bleeding Splenectomy is curative
Pseudoaneurysm	Enzymatic digestion of arterial wall	Bleeding	Urgent EGD CT Angiography	Angiographic embolization Surgery, if embolization fails
Pancreatic cancer	Highest risk in active smokers	No specific symptoms Abdominal pain, weight loss, jaundice	CA19-9 CT EUS	Surgery, if resectable

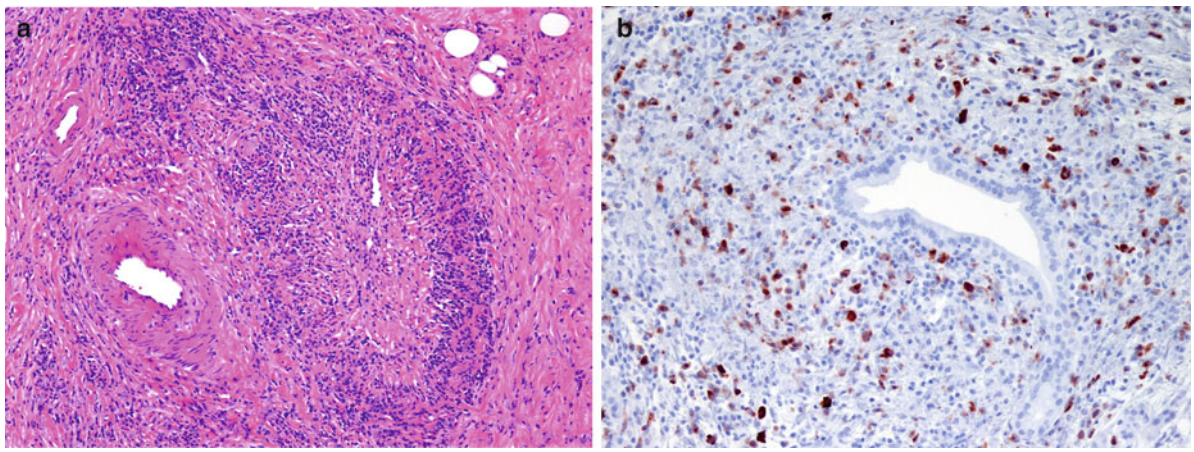

Fig. 44.5 Histopathololologic findings of autoimmune pancreatitis type I. (**a**) H & E stain shows lymphoplasmacytic infiltrate and storiform fibrosis surrounding a vein (obliterative phlebitis). (**b**) IgG4 immunostain shows diffuse increase in IgG4 in the gland

(affecting males and females equally). Type 2 disease rarely relapses or manifests with extrapancreatic disease but is associated with inflammatory bowel disease in 20–30% cases [52]. AIP typically presents with obstructive jaundice. Other manifestations include a pancreatic mass (at times mistaken for a carcinoma) and other organ involvement (sialadenitis, retroperitoneal fibrosis, lymphadenopathy, interstitial nephritis, etc.) [53]. The HISORt criteria (*H*istology, characteristic *I*maging (Fig. 44.6), elevated IgG4 on *S*erology, *O*ther organ involvement, *R*esponse to *t*reatment) are commonly used for diagnosis [54]. For inconclusive cases, a pancreatic biopsy might be necessary. Steroids are the mainstay of treatment. Patients who relapse on steroids or following steroid withdrawal may require immunosuppression (azathioprine, mycophenolate, cyclophosphamide, etc.) [53].

Key Points

- While alcohol is the most common cause of chronic pancreatitis in the general population, alcoholic pancreatitis rarely has its onset over age 60 years.
- Pancreatic cancer can mimic chronic pancreatitis in the elderly.
- There might be a latency of decades before chronic pancreatitis becomes clinically evident.

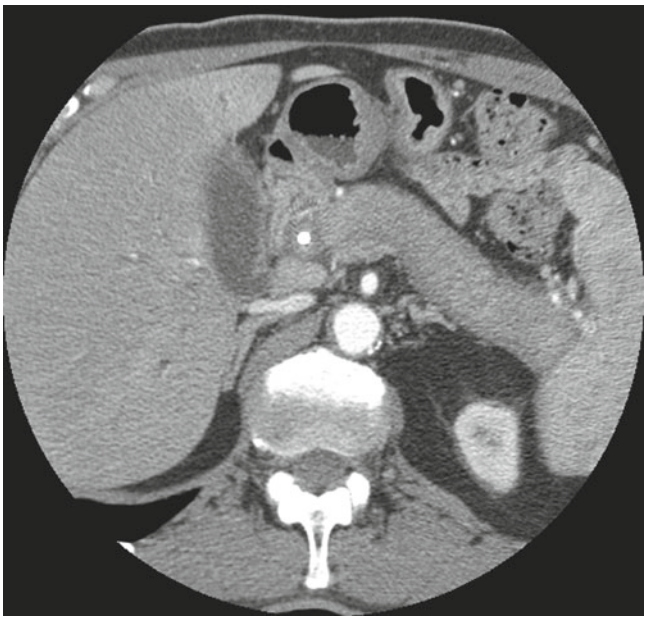

Fig. 44.6 Contrast-enhanced high resolution CT scan in a patient with autoimmune pancreatitis shows a diffusely enlarged gland with a rim like enhancement. This patient also had biliary involvement and underwent stent placement which is evident in this image

- Elderly patients often present with exocrine insufficiency without significant abdominal pain.
- Age-related changes in pancreatic structure can resemble the changes of chronic pancreatitis.
- Diffuse pancreatic calcifications on abdominal radiographs are specific for chronic pancreatitis but are generally seen in late stages of the disease.
- In early chronic pancreatitis, CT and MRI may be normal.
- EUS findings of chronic pancreatitis may be confounded by changes due to aging, alcohol, and smoking.
- Patients with chronic pancreatitis are at increased risk of pancreatic cancer.

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