Chronic Pancreatitis

Michelle Stram, MD, Shu Liu, PhD, Aatur D. Singhi, MD, PhD*

KEYWORDS

• Pancreas • Etiology • Pathology • Alcohol • Obstruction • Paraduodenal • Autoimmune • Hereditary

Key points

- Chronic pancreatitis is a progressive, fibroinflammatory disease characterized by irreversible damage to the pancreas.
- The underlying cause of chronic pancreatitis is multifactorial and involves a complex interaction of environmental, genetic, and/or other risk factors.
- The pathology of chronic pancreatitis is highly variable and dependent on the pathogenesis of the disease.
- The main differential diagnosis of chronic pancreatitis is pancreatic ductal adenocarcinoma and differentiating between these 2 entities remains a significant clinical and diagnostic challenge.

ABSTRACT

Chronic pancreatitis is a debilitating condition often associated with severe abdominal pain and exocrine and endocrine dysfunction. The underlying cause is multifactorial and involves complex interaction of environmental, genetic, and/or other risk factors. The pathology is dependent on the underlying pathogenesis of the disease. This review describes the clinical, gross, and microscopic findings of the main subtypes of chronic pancreatitis: alcoholic chronic pancreatitis, obstructive chronic pancreatitis, paraduodenal ("groove") pancreatitis, pancreatic divisum, autoimmune pancreatitis, and genetic factors associated with chronic pancreatitis. As pancreatic ductal adenocarcinoma may be confused with chronic pancreatitis, the main distinguishing features between these 2 diseases are discussed.

OVERVIEW

Chronic pancreatitis was first reported in the medical literature by Sir Thomas Cawley in 1788.[1] He described a "free living young man" who died of diabetes and on autopsy was found to have a pancreas filled with calculi. Since this landmark publication, there have been major advances in our understanding of the pathogenesis and pathophysiology of chronic pancreatitis that include etiologic risk factors, natural history, and associated genetic changes. Based on numerous studies, chronic pancreatitis is considered to be a progressive, fibroinflammatory disease characterized by irreversible damage to the pancreas.[2] In the United States, the overall incidence of chronic pancreatitis ranges from 4.4 to 11.9 cases per 100,000 per year, and the prevalence ranges from 36.9 to 41.8 cases per 100,000.[3–5] Patients often present with severe abdominal pain and both exocrine and endocrine dysfunction. Treatment for chronic pancreatitis is mostly supportive and, thus, patients repeatedly seek medical attention, which strains medical resources and represents a huge financial burden. In fact, despite the low prevalence of chronic pancreatitis within the United States, it ranks seventh for hospital admissions, and eighth for overall costs among digestive diseases.[6] Moreover, patients with longstanding chronic pancreatitis are at increased risk for developing pancreatic ductal adenocarcinoma.[7] The underlying cause of chronic pancreatitis is multifactorial and involves a complex interaction of environmental, genetic, and/or other risk factors.[2,8] The

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Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
* Corresponding author. UPMC Presbyterian Hospital, 200 Lothrop Street, Room A616.2, Pittsburgh, PA 15213.
E-mail address: singhiad@upmc.edu

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pathology of chronic pancreatitis is equally intricate and can vary significantly based on the pathogenesis of the disease. Herein, we review the key clinical and pathologic features of the major subtypes of chronic pancreatitis. Further, as chronic pancreatitis may closely mimic pancreatic ductal adenocarcinoma, we discuss their distinguishing features.

ALCOHOLIC CHRONIC PANCREATITIS

BACKGROUND

In western countries, heavy and prolonged alcohol use is a major cause of chronic pancreatitis. Patients are typically young-to-middle aged (30–50 years) men, who develop chronic pancreatitis after repeated attacks of acute pancreatitis as they continue to drink.[9] Interestingly, fewer than 5% of alcoholic individuals develop chronic pancreatitis. This observation implies the involvement of additional insults or factors. In fact, smoking, a high-fat diet, obesity, genetics, and infectious agents have been suggested to contribute to pancreatic disease in alcoholic individuals.[9–11] Similar to other etiologies of chronic pancreatitis, alcoholic chronic pancreatitis is clinically characterized by frequent episodes of epigastric/abdominal pain in the early stages of the disease. Over time, the pain attacks decrease in frequency and intensity, which parallel the progressive destruction of the gland and eventual endocrine and exocrine insufficiency. Patients with this disease have an elevated risk of pancreatic ductal adenocarcinoma, but comparable to other forms of chronic pancreatitis.

Key Points

- In western countries, heavy and prolonged alcohol use is a major cause of chronic pancreatitis.
- Patients are typically young-to-middle aged (30–50 years) men.
- Fewer than 5% of alcoholic individuals develop chronic pancreatitis which implies the involvement of additional cofactors.
- Gross and microscopic findings consist of progressive perilobular and interlobular fibrosis with ductal dilatation, distortion and squamous metaplasia.
- Advanced cases include intralobular fibrosis, pseudocyst formation, and intraductal calculi.

GROSS FEATURES

The gross findings of alcoholic chronic pancreatitis can differ in the early and late stages of this disease.[12] Early alcoholic chronic pancreatitis commonly shows an uneven distribution of perilobular and interlobular parenchymal fibrosis. On cut surface, these findings impart an indurated appearance to the gland with variation in size and accentuation of individual pancreatic lobules. The pancreatic ducts in affected areas, which are often embedded in fibrosis, display dilatation and/or distortion. Pseudocysts may be encountered, but are small and located within the periphery of the pancreatic body and tail.

In the latter stages of alcoholic chronic pancreatitis, the pancreas appears opaque, shrunken, and reduced in size due to parenchymal atrophy and continuing fibrosis. There is extensive loss of normal pancreatic lobular architecture with replacement by diffuse fibrosis.[13] Pancreatic ductal changes are also more prominent and range from obstruction to overt dilatation and/or distortion (**Fig. 1**A). Calculi, which are composed of calcium carbonate, are frequently present within the main pancreatic duct and branch ducts, and vary in size from 0.1 cm to larger than 1.0 cm in diameter. Pseudocysts are present in 25% to 50% of cases and can exceed 10 cm in greatest dimension (**Fig. 1**B).[14] They are filled with turbid, necrotic debris, which is rich in exocrine enzymes. In some cases, pseudocysts may connect to the ductal system, erode through major vessels, or rupture within the retroperitoneum.

MICROSCOPIC FEATURES

Analogous to the gross findings, microscopic examination of early alcoholic chronic pancreatitis reveals perilobular and interlobular fibrosis, which is composed of scattered, spindled fibroblasts and thin wavy collagen (**Fig. 2**A, B).[12,13] A patchy distribution of T-cell lymphocytes, plasma cells, and macrophages are frequently associated with these areas of fibrosis. The intralobular ducts are focally dilated and/or distorted, and contain intraluminal proteinaceous plugs. In addition, the ductal epithelium may be hyperplastic or undergo squamous metaplasia. Foci of resolving fat necrosis characterized by partially necrotic adipose tissue with foamy macrophages, multinucleated giant cells, and chronic inflammation also may be present.

In advanced cases, there is extensive loss of pancreatic acinar, ductal, and islet cell parenchyma with replacement by not only perilobular and interlobular fibrosis, but also intralobular