ABSTRACT

Recent advances in chronic pancreatitis have demonstrated it as a heterogeneous group of disease with various etiologies, such as alcohol related chronic pancreatitis, autoimmune mediated pancreatitis, hereditary pancreatitis and idiopathic pancreatitis. Correct classification based on thorough history and workup is important, e.g. autoimmune mediated pancreatitis can present with abdominal pain and pancreatic mass therefore mimicking a pancreatic malignancy. This review mainly focuses on the recent advances on the histopathological changes, diagnosis, etiology, treatment as well as serum/tissue biomarker research and animal models.
INTRODUCTION

Chronic pancreatitis is a fibro-inflammatory process in pancreas leading to exocrine insufficiency. It is a disease that relatively low in incidence, however has significant morbidity. The annual incidence of chronic pancreatitis ranges from 7.8[1] to 12/100,000 [2] and the prevalence ranges from 26.4 [3] to 36.9/100,000 persons [2]. Clinically, it can be difficult to diagnose and manage. There has been a recent proposal to move from the definition of “a continuing inflammatory disease of pancreas, characterized by irreversible morphological change, and typically cause pain and/or permanent loss of function” that is based on morphology to a mechanistic definition of “Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop pathologic response to parenchymal injury or stress” for early diagnosis [4]. As the authors pointed out, this new definition should be debated until consensus is reached.

Classification

A number of classification systems were proposed, with the most recent and commonly used etiologic classification being Toxic Idiopathic Genetic Autoimmune Recurrent Obstructive (TIGAR-O) system, based on the major predisposing risk factors: (1) toxic-metabolic, (2) idiopathic, (3) genetic, (4) autoimmune, (5) recurrent and severe acute pancreatitis, or (6) obstructive [5].

Etiology and Pathogenesis

The most common cause of chronic pancreatitis in developed countries was considered to be alcohol; however, alcohol-related pancreatitis is likely to be a multifactorial disease since chronic pancreatitis developed in only less than 10% of chronic alcoholics [6]. Tobacco has been shown to be an independent risk factor for developing chronic pancreatitis [7]. Genetic factors may also play a role. Single nucleotide polymorphism at PRSS1-PRSS2 loci (PRSS1 is the gene for cationic trypsinogen and PRSS2 is the gene coding for anionic trypsinogen) was found to have association with alcoholic chronic pancreatitis in a European study [8].

Hereditary pancreatitis is an autosomal dominant disorder and was first described in 1952 [9]. The first Paper Reporting Responsible Gene (PRSS1) mutation was published in 1996 [10]. Mutation within the PRSS1 geneis found in vast majority of the hereditary pancreatitis cases. The mutation is usually a gain of function point mutation.

Idiopathic pancreatitis is a diagnosis of exclusion of other potential causes. Due to the recent understanding of hereditary and autoimmune pancreatitis, number of true idiopathic pancreatitis cases is expected to decline with through history and genetic workup. An extensive review on this topic is available [11].
Except primary chronic pancreatitis, a significant amount of chronic pancreatitis is secondary to proximal end of the duct obstruction. Obstructive pancreatitis can be caused by various factors, such as duodenal wall cyst, ampullary tumor, intraductal carcinoma, ectopic pancreatic tissue [12] and pancreatic neoplasm including both exo and endocrine tumors [13,15]. It is always important to search for the malignancy if there is chronic pancreatitis present.

**Histopathological Change**

Histology is the gold standard for diagnosis of chronic pancreatitis, and the hallmark is fibrosis. Alcohol-related pancreatitis show varying degrees of parenchyma atrophy with calcification and fibrosis [15]. Chronic pancreatitis can be diffuse or focal, which mimics neoplasm clinically or radiographically. Most chronic pancreatic show loss of acinar structure, small ductal proliferation, lymphocytic dominant stromal inflammation, stromal fibrosis; and commonly show endocrine islets proliferation Figure 1 Accompanied low grade Pancreatic Intraepithelial Neoplasia ([PANIN](#)) is commonly seen. Differentiating chronic pancreatitis from pancreatic adenocarcinoma is important. Loss of the lobular architecture, significant cytological atypia, infiltrative pattern, the presence of perineural or angiolymphatic invasion is all directing to a malignant process. However, currently, there is none specific marker that can differentiate chronic pancreatitis form cancer readily. A variety of markers are available including P53, SMAD4, mesothelin, and CRABPII etc [16]. The diagnosis is still an H&E based morphological diagnosis with the help of many accessory tools.

**Figure 1:** Histology of focal chronic pancreatitis. Upper panel, at lower magnification (x40), showing acinar structure damage, ductal proliferation, lymphocytic inflammation in stroma, and neuroendocrine islet proliferation. Lower panel, at higher magnification (x100), islet proliferation.
Autoimmune pancreatitis is a special form of chronic pancreatitis and subdivided into type 1 and type 2, which have different clinical presentation, serology markers and histological presentations. For type 1 AIP, according to Zhang et al [17], pancreatic tissue show moderate or marked infiltration by IgG4-positive plasma cells in 16/17 type 1 AIP while 8/9 chronic alcoholic pancreatitis had no or mild stains. For Type 2 AIP, the most distinctive feature was reported to be a dense periductal collar of lymphocytes and plasma cells with neutrophilic microabscessed within the lumen of the duct, termed granulocytic epithelial lesion [18]. A recent study compared neutrophil infiltration in the pancreatic duct and found that the count of neutrophils around pancreatic ducts were significantly higher in type 2 AIP than type 1 AIP and alcoholic chronic pancreatitis [19]. For hereditary chronic pancreatitis, there is a report of case series with 10 cases with heterogenous germline mutation in PRSS1. In pediatric patients, patchy parenchymal loss and fibrosis with a mild increase in chronic inflammation was seen. In adults, the pancreas showed progressive atrophy and replacement by mature adipose tissue, with scattered nerves and islets of Langerhans in older adults [20].

**Diagnosis**

Although histology remains the gold standard for the diagnosis, biopsy is usually not available unless associated pancreatic malignancy was suspected. The practical and efficient way of diagnosis of chronic pancreatitis can be drawn from clinical history, imaging studies and functional tests [21]. Various imaging procedures can be used to evaluate pancreatic disease, including (CT) Computed Tomography, (ERP) Endoscopic Retrograde Pancreatography, (EUS) Endoscopic Ultrasonography and (MRI) Magnetic Resonance Imaging.

Autoimmune pancreatitis (AIP) is a rare disorder that is challenging to diagnosis because the clinical presentation can be difficult to distinguish from other more frequent forms of pancreatitis and malignancy. There are certain common characteristic features found in imaging study for AIP but they are not present in all of the cases [22]. Local AIP can mimic cancer and result in unnecessary resection of pancreas [23,24]. There are two clinical subtypes of AIP [25]. Type 1 is IgG4 related and is the pancreatic manifestation of systemic disease. Majority of the patients have elevated IgG4 plasma levels and IgG4 positive plasma cell infiltrates, although there is case report of patient with manifestation fulfilling criteria of type 1 AIP without elevated levels of serum IgG4. Type 2 AIP is not associated with increased serum IgG4 and often associated with Crohn’s disease and ulcerative colitis [26].

**Serum and Tissue Biomarker/Profiling**

Due to the risk of performing and challenge of interpreting pancreatic biopsy, a biomarker with high sensitivity and specificity to distinguish pancreatitis and pancreatic cancer would be invaluable for clinical practice. There are various study on useful serum biomarkers to help distinguish autoimmune pancreatitis and pancreatic cancer, such as serum gelatinase levels [28], alteration of serum N-glycan profile [29]. There is study on mRNA expression on pancreatic...
specimen and there is report that mRNA expression of Col11A1 is expressed at higher level in adenocarcinoma of the pancreas compared to chronic pancreatitis (5.25 fold higher, p=0.006) [30]. There has also been paper published on using serum gas chromatography mass spectrometry (GC/MS) [31] or electrospray-mass spectrometry Profiling To Distinguish Early-Stage Pancreatic Adenocarcinoma (PDAC) from pancreatitis [32], although a specific biomarker is yet to be found. Formalin-Fixed And Paraffin-Embedded (FFPE) human tissue has been the subject of global proteomic study of chronic pancreatitis [33]. The authors identified three proteins with significant increase in disease vs normal. Immuno Histo Chemistry (IHC) results confirmed that lumican; extracellular protein matrix proteoglycan is up-regulated in both mild and severe chronic pancreatitis while another proteoglycan, versican, is increased in severe chronic pancreatitis and PDAC. Another group of scientists analyzed 9 FFPE pancreatic tissue specimens including normal (n=3), chronic pancreatitis (n=3), and pancreatic cancer (n=3) [34]. Proteins only identified in chronic pancreatitis specimens were collagen alpha-1 (XIV), filamin A, collagen alpha-3 (VI), and SNC73. KEGG pathway analysis found that collagen alpha-3 (VI) and filamin A were involved in the focal adhesion pathway. More recent proteomics studies of pancreatitis including studies on animal models were summarized in another review paper [35].

ASSOCIATION WITH PANCREATIC ADENOCARCINOMA AND GENERAL MALIGNANCY

The relative risk of pancreatic adenocarcinoma in patients with chronic pancreatitis has been reported to be high, with the incidence ratio being 19.0 in a prospective single center cohort of 373 patients compared to expected number of cases based on cancer registery [36]. This study does not include AIP and the four cases of patients developed pancreatic adenocarcinoma include three cases of alcoholic chronic pancreatitis and one case of idiopathic chronic pancreatitis. For AIP, an excellent review is available discussion current knowledge about AIP and risk of general malignancy [37]. There are multiple studies indicating that AIP patients are at increased risk of having pancreatic cancer. One single center study monitored development of type 1 AIP and pancreatic cancer and the incidence rate of cancer development is comparable between AIP group and ordinary chronic pancreatitis group, which would suggest that surveillance is also needed for AIP patients [38]. A multicenter retrospective cohort study found the standardized relative risk ratio for cancer diagnosis is 2.7 interestingly, majority of the cancers are found in other organ, such as stomach, lung, thyroid and colon, and only one patient out of 15 patients had bile duct cancer. For patient with concurrent IgG4 related disease and malignancy, paraneoplastic syndrome (i.e, the IgG4 is secondary to the malignancy) is a possibility suggested by the authors [39]. Therefore, the association of AIP and pancreatic adenocarcinoma is still debatable.

Animal Models

Various rodent animal models have been developed for chronic pancreatitis, such asLPS/ alcohol induced rat model [40], tobacco smoke induced rat model [41], toxin (dibutyltin...
dichloride) injection induced rat model [42], ductal obstruction induced rat model [43]. A number of genetically modified animal models have been developed as well, such as a BK5 promoter driven COX-2 transgenic mice model demonstrated first chronic pancreatitis-like state and then dysplastic changes in pancreatic ducts [44]. An insulin II promoter driven TGF-β1 transgenic mice showed pancreatic fibrosis with extracellular matrix deposition from 70 days old [45]. Immune-related models corresponds to AIP have also been found, including a strain of mice (MRL/Mp-+/+) that develop chronic pancreatitis spontaneously at 34-38 weeks [46] and the process can be accelerated by polyinosinic: polycytidyllic acid injection [47]. An extensive review on animal model for pancreatitis is available [48]. At current time; whether these models fully recapitulate the human disease remain unclear.

**TREATMENT**

The treatment depends on etiology and stage of the disease. The mainstay therapy for AIP is corticosteroid [49,50] based on observational data since there has not been a randomized controlled clinical trial conducted. In patients intolerant of steroids or experiencing relapse with therapy, rituximab and immunomodulator have been shown to be effective in the treatment of AIP [51]. For chronic pancreatitis caused by other etiology, nutrition and life style changes, medical management of pain, exocrine and endocrine insufficiency and surgical treatment is usually employed as last resort [21].

**CONCLUSIONS**

Chronic pancreatitis is a heterogenous group of disease from aspect of etiology. The successful treatment is dependent on the correctly identifying the etiology, and some of the chronic pancreatitis are medically treatable. Autoimmune pancreatitis is particularly important to recognize due to possible confusion with pancreatic malignancy and result in unnecessary pancreatectomy, and also this group of patient could respond well to immunomodulation therapy. Among type 1 and type 2 autoimmune pancreatitis, type 2 may be more challenging to diagnosis due to lack of elevated serum IgG4 and overlapping histology features with alcohol related chronic pancreatitis. Serum and tissue markers as well as profiling for chronic pancreatitis have been reported, and a clinically useful marker with high sensitivity and specificity is to be found. Hereditary pancreatitis is a rare entity that needs to be recognized due to lack of effective therapy.

**References**


