Pancreatitis

Professor Fiona Campbell
Consultant Gastrointestinal Pathologist
Royal Liverpool University Hospital
F.Campbell@liverpool.ac.uk

Sarajevo, November 2015

Chronic pancreatitis

- **Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas, which leads to irreversible morphological changes (parenchymal atrophy & fibrosis) and impairment of exocrine and endocrine function**
- **Alcohol overconsumption is most frequent cause (70%)**
- **But 90% of alcoholics never get CP**
- **Genetic predisposition & environmental factors**
- **25% of cases are idiopathic**
- **Several classification schemes have been proposed, each with different focus on clinical, imaging and morphological features**

Classification of chronic pancreatitis

Table 2. Classification proposal for pancreatitis based on the main clinical, morphological, and etiological features*

Clinical presentation	Outcome	Morphology	Diagnosis
Background of alcohol abuse			
Mild episode of acute pancreatitis	Recovery	Small foci of fat necrosis	Alcoholic mild acute pancreatitis
Severe episode of acute pancreatitis	With systemic complications	Extensive fat and hemorrhagic necrosis	Alcoholic severe acute pancreatitis
Relapsing episodes of acute pancreatitis	Recurrent pain	Focal perilobular fibrosis, pseudocyst	Alcoholic early stage chronic pancreatitis
Permanent pain, maldigestion	Functional insufficiency	Diffuse perilobular fibrosis, pseudocyst, calculi	Alcoholic advanced chronic pancreatitis
Background of gallstone disease			
Mild/severe episode of acute pancreatitis	Without/with local and systemic complications	Like alcoholic acute pancreatitis	Biliary acute mild/severe pancreatitis
Background of hereditary, familial pancreatitis			
Mild/severe episode of acute pancreatitis	Recurrent pain	Like alcoholic acute pancreatitis	Hereditary acute mild/severe pancreatitis
Relapsing episodes of acute pancreatitis	Functional insufficiency	Perilobular and periductal fibrosis, duct dilatation, calculi	Hereditary chronic pancreatitis
Background of shock or drug intake			
Mild/severe episode of pancreatitis	Pain, systemic complications	Like alcoholic acute pancreatitis	Shock/toxic pancreatitis
Background of hypergammaglobulinemia/IgG4 elevation			
Jaundice, pain	Stenosis of common bile duct, stenosis of pancreatic duct	Periductal lymphoplasmacytic infiltration, sclerosis	Autoimmune pancreatitis
Background of hypercalcemia/hyperlipidemia			
Mild and severe episodes of acute pancreatitis	Recovery or local complications	Like alcoholic acute pancreatitis	Metabolic pancreatitis
Relapsing episodes of acute pancreatitis		Perilobular fibrosis, pseudocyst	
Background of viral/bacterial infection			
Mild episodes of acute pancreatitis	Recovery	Scattered acinar necrosis	Infectious acute pancreatitis
Background of alcohol abuse			
Vomiting, nausea, episodes of acute pancreatitis, jaundice	Duodenal stenosis, common bile duct stenosis	Cystic and chronic inflammatory changes in the duodenal wall at the minor papilla	Paraduodenal pancreatitis

*Because idiopathic pancreatitis is by definition not associated with a special etiology, it is not considered in this classification

Klöppel G. J Gastroenterol 2007; 42 (suppl 17): 55-57

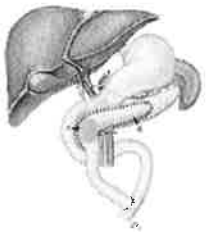
Surgical resections for CP

- Performed for intractable pain in late-stage disease
- Specimens of 'burnt-out' chronic pancreatitis with scanty inflammatory cell infiltrate, almost completely absent pancreatic parenchyma, and marked fibrous tissue
- Extensive tissue sampling to exclude malignant transformation in CP
- Frey, Beger & Peustow procedures: aim to decompress the pancreatic duct system, which is thought to be a major cause of pain in CP

Aimoto et al. J Nippon Med Sch 2011; 78: 352-9

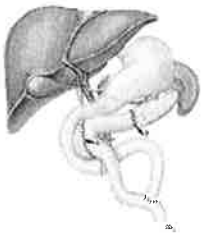
Frey procedure

- Core out 4-12g of diseased tissue from pancreatic head, leaving a 'tissue crater'. Jejunal loop is anastomosed over the tissue crater and longitudinally opened pancreatic duct



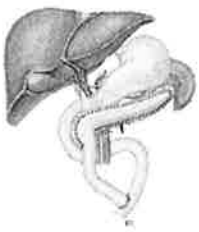
Beger procedure

- Most of head and part of body of pancreas are resected, leaving thin crescent of head and the intrapancreatic CBD in situ. Jejunal loop is anastomosed on the transection margins of the remnant head and body



Puestow procedure

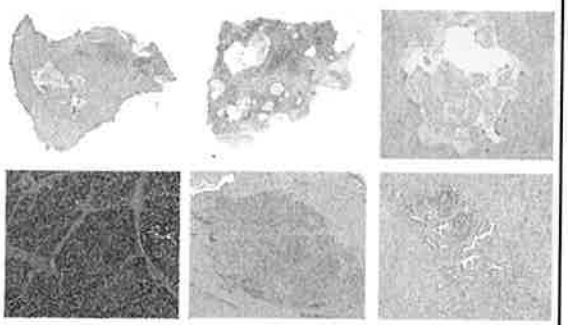
- Expose main pancreatic duct from neck to tail. Jejunal loop is anastomosed to anterior pancreatic surface to allow drainage of main and secondary pancreatic ducts over a length of 8-10cm



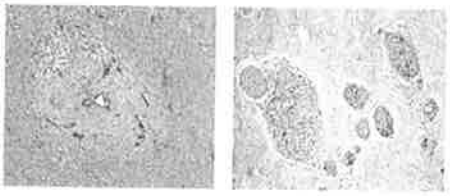
Chronic pancreatitis

- Diffuse or localised
- Early stages, pancreas indurated and enlarged
- Later stages, rock hard and shrunken
- Duct dilatation/calculi
- Calcified deposits in pancreas or peripancreatic tissue, due to calcification in previous fat necrosis
- Pseudocysts

Chronic pancreatitis - microscopy

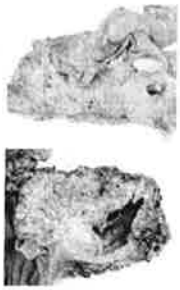


Chronic pancreatitis - microscopy



Pseudocysts

- Collection of pancreatic juice secondary to duct rupture
- Occur in acute and chronic pancreatitis
- Thin walled in acute pancreatitis, thicker wall in chronic pancreatitis
- Unilocular, fluid-filled, no septations/ mural nodules/ excrescences
- No epithelial lining
- Granulation tissue and (over time) fibrosis



Pseudocyst

Pancreatitis

- Autoimmune pancreatitis
- Groove pancreatitis/ paraduodenal pancreatitis
- Hereditary chronic pancreatitis

Autoimmune pancreatitis (AIP)

- Concept of AIP introduced in 1995
- Sclerosing chronic pancreatitis or non-alcoholic duct destructive chronic pancreatitis
- Chronic fibroinflammatory disease
- Autoimmune pathogenesis, but cause unclear
- Responds to steroid therapy

  Shimosegawa et al. Pancreas 2011; 40: 352-8
- Spontaneous regression in 40% of AIP

  Kubota et al. Gastrointest Endosc 2007; 66: 1142-51
- 10% of patients with chronic pancreatitis

Autoimmune pancreatitis

- Clinically: abdominal pain (less severe than in other forms of CP), weight loss, obstructive jaundice
- PDAC is main clinical differential diagnosis
- Imaging: diffuse sausage-shaped enlargement with rim enhancement or focal lesion
- Heterogeneous disease with 2 subtypes: type 1 AIP (more common worldwide) and type 2 AIP, which have distinct clinical and histological features

  Chari et al. Pancreas 2010; 39: 549-54

  Shimosegawa et al. Pancreas 2011; 40: 352-8

  Zhang et al. Pancreas 2011; 40: 1172-9

  Deshpande et al. Mod Pathol 2012; 25: 1185-92

Autoimmune pancreatitis

	Type 1 AIP	Type 2 AIP
Age of presentation	7th decade	5th decade
Gender distribution	predominantly male	equal
Presentation:		
- obstructive jaundice	75%	50%
- acute pancreatitis	15%	33%
Imaging:		
- diffuse sausage-like swelling, ↓on enhancement	40%	15%
- focal changes	60%	85%
Elevated IgG4:		
- serum	usually	no
- tissues	usually	scarce
Extra-pancreatic organ involvement	yes	no
Associated idiopathic inflammatory bowel disease	2-5%	up to 30%
Disease relapse	common	rare

Adapted from Raghuwansh & Chari. Curr Gastroenterol Rep 2012; 14: 95-105

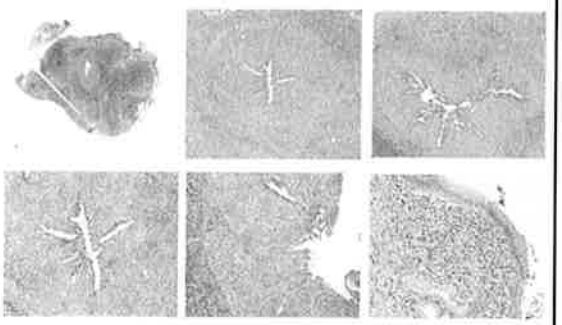
AIP - macroscopy

- Diffusely enlarged pancreas
- Loss of normal lobulation
- May be only focal involvement – mass
- Narrowing of pancreatic duct
- Intrapancreatic CBD may also be narrowed
- Peripancreatic LNs may be enlarged

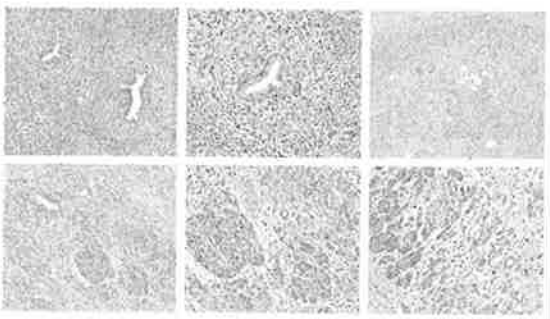
AIP - microscopy

- Periductal lymphoplasmacytic infiltrate (narrowed, star-shaped duct lumen)
- Inflammation of acinar parenchyma
- Patchy distribution of the inflammatory changes

Autoimmune pancreatitis



Autoimmune pancreatitis



Type 1 AIP - microscopy

- Storiform fibrosis
- Fibro-inflammation extends into peripancreatic tissue
- Obliterative phlebitis, which probably starts as a perivenulitis
- Lymphoid aggregates
- IgG4 plasma cells

Type 2 AIP - microscopy

- Granulocytic epithelial lesion (GEL)
  Klöppel G. Mod Pathol 2007; 20: S113-31
- Scanty or absent IgG4 plasma cells

IgG4 immunostaining

- Different threshold values ranging from >10 to >50 IgG4+ plasma cells/hpf have been proposed
- >10/hpf for biopsies, >50/hpf for resection specimens
- Distribution of IgG4+ plasma cells is patchy
- Count best performed in 'hot spot'
- Average counted in three x40 objective microscopic fields within the hot spot
- Low count not exclude AIP; patchy distribution, evolving fibrosis, previous steroids
- IgG4+/IgG+ ratio of >40%, recommended cut off value
- IgG/IgG4 IHC on biopsy from major papilla

Moon et al. Gastrointest Endosc 2010; 71: 960-6

AIP - frozen section

Groove pancreatitis

- Cystic dystrophy of the duodenal wall / para-ampullary duodenal wall cyst/ cystic dystrophy of heterotopic pancreas/ paraduodenal pancreatitis
- Mass between the head of the pancreas and the second part of the duodenum in pancreatoduodenal groove
- Due to presence of ectopic pancreas in wall of duodenum between ampulla of Vater and minor papilla

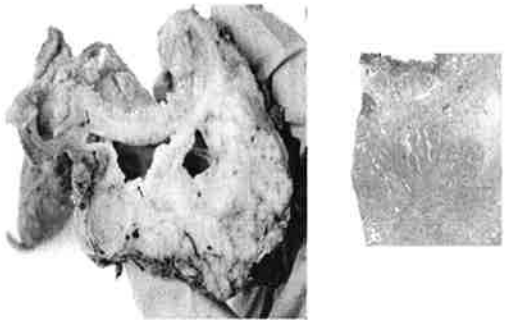
Groove pancreatitis

- Drainage of pancreatic secretions from ectopic tissue is impaired; duct dilatation, cyst formation and rupture, inflammation
- Chronic alcohol consumption is a further pathogenetic factor, increasing pancreatic secretions in the ectopic pancreas
- Both pathogenetic factors needed; explains rarity of condition, despite ectopic pancreas in duodenal wall being common

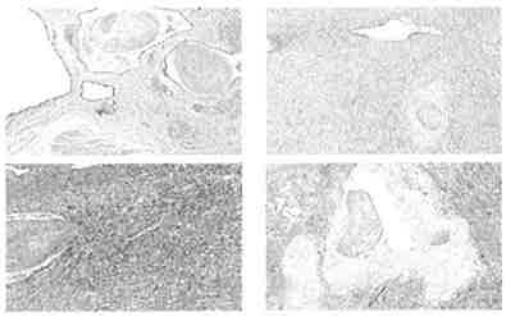
Groove pancreatitis

- Young to middle-aged male adults with a history of alcohol abuse
- Present with abdominal pain, nausea & vomiting due to duodenal stenosis, weight loss
- EUS – multiple cysts within thickened duodenal wall
- Differential diagnosis – PDAC
- Macroscopy – cystic spaces in thickened duodenal wall and in pancreatoduodenal groove; can extend into pancreas
- Irregular duodenal mucosa with hyperplasia of Brunner's glands

Groove pancreatitis



Groove pancreatitis



Groove pancreatitis

Hereditary chronic pancreatitis

- Described in 1952 as 'hereditary chronic relapsing pancreatitis'

  Comfort & Steinberg. Gastroenterology 1952; 21: 54-63
- Rare form of chronic pancreatitis (1-2 % of cases)
- Autosomal dominant, 80% penetrance, variable disease expression
- Initial presentation in children/young adults (<20yrs)
- Recurrent attacks of acute pancreatitis, which progresses to CP in about half of the patients
- Absence of other aetiological factors
- Increased risk of pancreatic cancer

  Gross et al. Am J Med 1962; 33: 358-64
  Otsuki et al. Pancreas 2004; 28: 200-6

Genetics of hereditary pancreatitis

- 1996, gene for HCP mapped to chromosome 7 (7q35)

  Whitcomb et al. Gastroenterol 1996; 110: 1975-80
  Pandya et al. Genomics 1996; 38: 227-30
  Le Bodic et al. Hum Mol Genet 1996; 5: 549-54
- 1996, Whitcomb *et al* identified R122H mutation in exon 3 of the protease serine 1 (*PRSS1*) gene which encodes cationic trypsinogen

  Whitcomb et al. Nat Genet 1996; 14: 141-45
- 1997, second mutation (N29I mutation) in *PRSS1* gene was discovered

  Gorry et al. Gastroenterol 1997; 113: 1063-8
- Now > 30 mutations in the *PRSS1* gene described
- 60-80% of patients with HCP have R122H or N29I gain-of-function mutations

Hereditary chronic pancreatitis

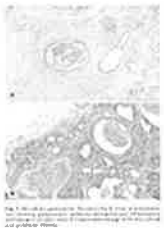
- No mutation been identified in other 20-40% of families
- Mutations in *PRSS1* gene are thought to prevent deactivation of inappropriately activated intrapancreatic trypsinogen or to increase trypsinogen activation, resulting in acinar cell autodigestion and subsequent pancreatitis

Diagnostic criteria for HCP

- Exclude other causes of CP in childhood, eg anatomical anomalies, metabolic disorders, cystic fibrosis, trauma, viruses
- Two first-degree relatives, or at least three second-degree relatives, in two or more generations, with recurrent acute pancreatitis and/or chronic pancreatitis, for which there are no precipitating factors
- Detection of p.R122H or p.N29I mutations in the *PRSS1* gene is diagnostic

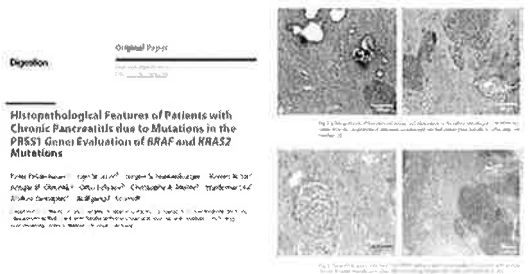
HCP - pathology

- Limited publications
- Dilated pancreatic ducts, protein plugs & calculi, periductal/perilobular fibrosis, pseudocysts
- PanINs
- Normal pancreas
- Extensive fatty infiltration



Klöppel G et al. Virch Arch 2004; 445: 1-8

Histological features of HCP

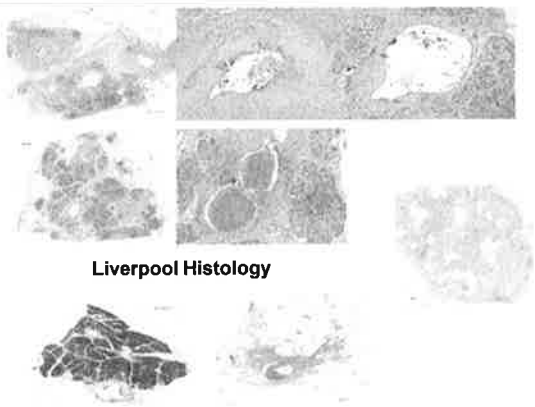


Digestion

Original Paper

Histopathological Features of Patients with Chronic Pancreatitis due to Mutations in the PRSS1 Gene: Evaluation of *BRAF* and *KRAS2* Mutations

Liverpool Histology



Histology of HCP

- 'PRSS1 hereditary pancreatitis is characterized by progressive lipomatous atrophy of the pancreas' (n=4)

Singhi AD et al. Am J Surg Pathol 2014; 38: 346-53

HCP – cancer risk

- Cancer risk with chronic inflammatory diseases
- First report of PDAC associated with HCP in 1958

Bartholomew et al. Gastroenterology 1958; 35: 473-7

- Patients with HCP have an estimated 50-fold increased relative risk for developing pancreatic cancer

Lowenfels et al. J Natl Cancer Inst 1997; 89: 442-6

- Develop PDAC at younger age than sporadic patients
- Up to 40% of HCP patients may develop PDAC
- No difference in risk of PDAC based on type of *PRSS1* gene mutation

Whitcomb DC. Am J Physiol Gastrointest Liver Physiol 2004; 287: 315-319

Rebours et al. Gut 2009; 58: 97-103

HCP – cancer risk

- Compare with 2-4 fold increased risk of PDAC with cigarette smoking, 2-20 fold increased risk in chronic alcoholic pancreatitis
- Smoking increases risk of PDAC in HCP, and seems to lower age of onset by nearly two decades

Lowenfels et al. JAMA 2001; 386: 169-70

- Avoid alcohol and do not smoke

Pancreatitis

- Chronic pancreatitis – sampling
- Autoimmune pancreatitis – periductal lymphoplasmacytic infiltrate; type 2 not associated with IgG4+ plasma cells
- Groove (or paraduodenal) pancreatitis – localised mass
- Hereditary chronic pancreatitis – PDAC at young age
- Peritumoural pancreatitis