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Diagnostic dilemmas

Chronic pancreatitis and pancreatic carcinoma

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Summary

The differential diagnosis between pancreatic cancer and chronic pancreatitis is very important as the management and prognosis of these two diseases is different. In most patients with pancreatic disease, the diagnosis can be established but there is a subgroup of patients in whom it is difficult to differentiate between these conditions because the clinical presentation is often similar and currently available diagnostic tests may be unable to distinguish between an inflammatory or neoplastic pancreatic mass. This paper reviews the aetiology, pathology and clinical features of these diseases and discusses the limitations of conventional diagnostic methods and how newer techniques may be of value in the differential diagnosis.

Keywords: diagnosis, chronic pancreatitis, pancreatic cancer

Aetiology of non-alcohol-induced chronic pancreatitis

- tropical: may be related to micronutrient deficiency
- hyperlipidaemia: may follow recurrent acute attacks of pancreatitis
- hyperparathyroidism: rare
- obstruction: benign obstruction of the main pancreatic duct
- trauma: obstructive in origin
- pancreas divisum: secondary to stricture of either the duct of Santorini or duct of Wirsung
- hereditary: autosomal dominant (rare)
- idiopathic: 10% of cases in the Western world; two distinct age bands occuring in the young and the elderly

Box 1

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The patient with pancreatic cancer requires early radical surgery if there is to be any hope of cure, whereas the patient with chronic pancreatitis, although requiring surgery in selected cases, will usually benefit from a period of conservative treatment, evaluation of aetiological factors, and assessment of disease progression. Yet, the clinical presentation of pancreatic cancer may sometimes be indistinguishable from that of chronic pancreatitis. Inflammatory changes commonly occur in association with a primary carcinoma, while an increased incidence of pancreatic carcinoma has been reported in association with long-standing chronic pancreatitis. This close relationship can make differentiation difficult even after detailed investigation. This article reviews the current knowledge of these conditions, and indicates how current and novel diagnostic techniques can be employed to reach an optimal management policy.

Aetiology

CHRONIC PANCREATITIS

Clinically apparent chronic pancreatitis is a rare condition with a prevalence of less than 30 per 100 000 and a yearly incidence of less than 10 per 10 000,[1] with a rising incidence in populations with a high alcohol intake. Johnson and Hosking[2] reviewed national statistics for chronic pancreatitis in England and Wales between 1960 and 1988. They reported a four-fold increase in hospital discharges for chronic pancreatitis in males from 9.7 to 43 per million population per year and a two-fold increase in females from 8.7 to 21.2 over this period. This was associated with a 50% increase in annual death rates from chronic pancreatitis and an increase in median alcohol consumption. A similar study from Finland reported a four-fold increase in alcohol consumption between 1960 and 1989 associated with a 26% increase in the incidence of chronic pancreatitis from 10.4 to 13.4 cases per 100 000 population.[3] This increase was only seen in males, however, and was associated with a reduction in overall mortality.

Alcohol consumption is a key aetiological factor in the development of chronic pancreatitis. Up to 85% of cases are associated with excessive alcohol consumption, and per capita consumption has been correlated with the incidence of the disease.[4] However, a higher incidence of chronic pancreatitis is found in Scandinavia than in Switzerland, for example, despite a lower overall consumption of alcohol, indicating the importance of additional aetiological factors, which include cigarette smoking,[5] and nutrition (box 1). Studies of patients with tropical pancreatitis implicate protein and micronutrient deficiencies,[6] which may be related to impaired clearance of free radicals. Patients with alcohol-induced pancreatitis may be deficient in zinc and selenium[7] which, along with cigarette smoking, may inhibit quenching of oxygen free radicals.

There has been considerable interest in the composition of the protein plugs which are frequently found in the pancreatic juice of patients with chronic pancreatitis. The major component of these plugs is a degraded form of pancreatic stone protein or lithostathine. It has been suggested that a decreased secretion of pancreatic stone protein may be the initial common pathway in the development of chronic pancreatitis.[8] This is supported by the impairment in acinar cell secretion of lithostathine by ethanol, decreased levels of lithostathine in the pancreatic juice of patients with chronic pancreatitis and the observation that lithostathine prevents calcium precipitation in saturated solutions. Other authors, however, have challenged the role of lithostathine, as they found that similar levels were secreted by patients with pancreatic cancer and chronic pancreatitis and found increased serum levels of lithostathine in patients with both acute and chronic pancreatitis.[9]

PANCREATIC CANCER

Pancreatic carcinoma has undergone a dramatic rise in incidence during the twentieth century, and is one of the commonest causes of death from cancer in many western countries. A recent study from England estimated an age standardised incidence of 8.4 per 100 000 in women and 10.1 per 100 000 in men.[10] The prognosis for patients with pancreatic cancer is generally poor, with an overall five-year survival of less than 0.4% which is largely due to most patients presenting with an advanced unresectable cancer. It must be emphasised that, within the spectrum of pancreatic cancer, there are a number of rarer tumour types with a far better prognosis. A tissue diagnosis should therefore be sought, even for seemingly advanced lesions.

The causes of adenocarcinoma of the pancreas are not known although, with the notable exception of alcohol, the same aetiological factors have been implicated. Tobacco smoking is associated with a marginally increased risk.[11] A high dietary fat intake has also been implicated by international correlation studies.[12] A genetic predisposition has been identified in a number of cancer family syndromes, the most common being hereditary nonpolyposis colorectal cancer.[13] A tendency to familial clustering has been identified,[14] but whether this is due to environmental factors common to family members or is truly genetic is not known. Patients with familial chronic pancreatitis have an increased incidence of pancreatic cancer, approaching 25%, implying that the same gene is implicated in both diseases.[15] In long- standing alcohol-related chronic pancreatitis there is a five- to six-fold increase in the risk of pancreatic adenocarcinoma.[5] Other suggested risk factors include excessive consumption of coffee, previous cholecystectomy or gastric surgery, and diabetes mellitus, but the evidence is at best speculative and requires further investigation.[16]

Cancer of the ampulla of Vater is not a true pancreatic tumour, but similarities in its presentation and site can make even histological differentiation from a pancreatic carcinoma difficult. These tumours are considerably less common than carcinoma of the pancreas and appear to have a different aetiology. The site of ampullary carcinoma is suggestive of an interaction between tumour promoters in biliary, duodenal, and pancreatic secretions. Ampullary tumours have been identified with increasing frequency in familial adenomatous polyposis,[17] and are now one of the commonest causes of late death in patients undergoing prophylactic colectomy. Ampullary cancers may cause a secondary obstructive pancreatopathy and there is little diagnostic difficulty in distinguishing them from chronic pancreatitis as they can be seen by side viewing duodenoscopy and biopsied, although they cannot always be distinguished from pancreatic ductal adenocarcinomas which invade or ulcerate into the peri-ampullary mucosa.

Pathology

PANCREATIC CANCER

Over 85% of true pancreatic cancers are of ductal cell origin,[18] and 80% of these occur in the head of the gland. It is these lesions which commonly present with obstructive jaundice because of the proximity of the main bile duct, and thereby may be detected at a relatively early and potentially resectable stage. Incidental pancreatic cancer has been identified in autopsy studies in 2% of individuals,[19] which is far higher than anticipated by epidemiological studies, suggesting there may be a long latency period for the development of pancreatic cancer. Papillary duct hyperplasia may represent a premalignant lesion but this is disputed.[20] Non-exocrine tumours of the pancreas account for up to 15% of all pancreatic neoplasms (box 2). Endocrine tumours make up about 2.5% of pancreatic tumours and may be uni- or multi-focal, but they are generally well demarcated and rarely result in any ductal obstruction or secondary pancreatitis. Lymphoma of the pancreas may account for up to 5% of lesions and are probably still best treated by resection if possible but they also respond to chemotherapy and therefore provide an important reason for attempting to obtain histological diagnosis for all radiologically unresectable tumours.

Well differentiated cancers show an intense desmoplastic reaction, commonly spreading directly into the lower bile duct, duodenum, pylorus and gastric antrum, superior mesenteric vein and portal vein and haematogenous spread occurs most commonly to the liver. Diffuse infiltration of the retroperitoneal fatty tissues, perineural sheaths and lymphatics also limit the effectiveness and feasibility of resection. The notion that multicentric tumours may occur in over 25% of cases, supporting total pancreatectomy as a therapeutic option, has been refuted by more recent histological studies.[21] A (unifocal) monoclonal cellular origin in at least 95% of cases is also indicated by the results of molecular analysis for K-ras mutations.[22]

Tumours of the pancreas

Ductal (>85%)
- adenocarcinoma: long-term survival rare
- cystadenocarcinoma: 50% 5-year survival

Acinar (5%)
- acinar cell carcinoma: long-term survival rare

Islet (2.5%)
- insulinoma: 10% malignant
- VIPoma: 50% malignant
- gastrinoma: 60% malignant
- glucagonoma: 60% malignant
- non-functioning: 60% malignant

Non-epithelial (5%)
- lymphoma: responsive to chemotherapy

Box 2

There are a number of different rarer ductal tumours, some of which carry a distinctly better prognosis than ductal adenocarcinoma. Cystic tumours are noteworthy as they can be confused with non-neoplastic pseudocysts, seen in association with chronic pancreatitis. Thus, biopsy of a pseudocyst wall should always be sent for histology when surgical drainage is contemplated. Mucinous cystic tumours are more common in women and are often situated in the body or tail of the pancreas. Larger lesions (>8 cm) are frankly malignant and secrete a number of tumour-associated antigens including CEA, CA125 and CA19-9.[23] Serous cystadenomas are more frequently seen in older women and may be associated with calcification[24] and have been reported in association with the inherited Von Hippel Lindau cancer syndrome.[25] These are usually benign[26] and do not usually secrete high levels of tumour-associated antigens.

CHRONIC PANCREATITIS

The principal pathological feature of chronic pancreatitis is the progressive development of fibrosis and atrophy of the parenchyma often associated with diffuse parenchymal calcification, ductal strictures and dilatation, and nonparenchymal cystic degeneration. Clinically these changes are associated with chronic relapsing pain and impaired endocrine and exocrine function. In most cases the disease involves the whole gland, but in about one third it is limited to a segment of the gland. In about 10% of cases the disease is limited to an inflammatory mass in the head of the gland[27] which is particularly likely to result in diagnostic uncertainty, because of concern about an underlying resectable tumour. The aetiology of pain in chronic pancreatitis is incompletely understood, but may include raised parenchymal or intraductal pressure, perineural fibrosis, local enzymatic activity and destruction of the perineural sheath exposing axons to cytokines released by the chronic inflammatory cell infiltrate.[28] Surgical relief of obstruction by the formation of a longitudinal pancreaticojejunostomy or by drainage of a pseudocyst can provide some pain relief in patients with limited parenchymal inflammatory disease.[29] Although radiological appearances loosely correlate with functional loss,[30] the correlation with pain is poor.

Clinical presentation

Anorexia, weight loss, abdominal pain and nausea are symptoms common to both chronic pancreatitis and pancreatic cancer but the frequency of these symptoms varies between the conditions (box 3). Pain is not a prominent feature of early cancer. Intractable epigastric pain, radiating through to the back and eased by sitting forward is seen in about one third of advanced cases of pancreatic cancer and mimics the pain observed in chronic pancreatitis.[31] Anorexia and weight loss frequently occur in chronic pancreatitis and are related to poor nutrition as well as malabsorption from pancreatic insufficiency.

Obstructive jaundice is classically associated with tumours of the head of the pancreas, but is also seen secondary to fibrosis in chronic pancreatitis or occasionally due to duct compression by a pseudocyst in around 15% of cases.

Investigations

A range of techniques are available for investigating diseases of the pancreas (box 4). Assessments of pancreatic exocrine and endocrine function are useful for evaluating chronic pancreatitis[32] and objectively quantifying disease

Clinical features of chronic pancreatitis and pancreatic cancer

Clinical presentation	*Chronic pancreatitis*	*Pancreatic cancer*
Pain	most common symptom at presentation	late feature which suggests advanced disease
Weight loss	very common, multifactorial	very common even in early disease
Jaundice	especially in disease of the head of the gland and may fluctuate (approx 15% of cases)	common presenting feature in tumours of the head of the pancreas (80% of cases) and usually progressive
Steatorrhoea	common even without jaundice	common but often not appreciated
Impaired glucose tolerance	common due to glandular destruction	present in up to 30% of cases but may reverse after resection

Box 3

progression, but have no role in differentiating chronic pancreatitis from malignant disease.

IMAGING

The first line of investigation is usually ultrasonography,[33] and is particularly effective at demonstrating dilatation of the bile ducts and the level of obstruction. Dilatation of both the pancreatic duct and the bile duct is present in up to 90% of malignancies at the time of investigation, but only about 20% of cases of chronic pancreatitis. The ducts are usually seen to narrow at a hypoechogenic lesion if a tumour is present and can be supplemented by the use of pulsed Doppler scanning of the portal blood flow which is abnormal in the presence of a sizable malignancy in the head of the gland.

Computed tomography (CT) is currently considered to be the gold standard for pancreatic parenchymal imaging. The identification of diffuse calcification, best seen on CT scanning, is the hallmark of chronic pancreatitis, but focal calcification is seen in association with carcinomas and can cause confusion. Furthermore, up to 20% of cases of chronic pancreatitis may not have macroscopic calcification. Atrophy of the pancreas is a useful diagnostic feature seen in chronic pancreatitis and is not commonly seen in association with tumours. The development of contrast-enhanced spiral CT scanning has further extended the use of this modality, by providing reconstructed images of the major vessels for the assessment of local tumour invasion. There remains difficulty in differentiating between inflammatory and neoplastic lesions and in the ability to identify lesions less than 2 cm in diameter.[34] Magnetic resonance imaging (MRI) with gadolinium enhancement may marginally improve the accuracy of assessing pancreatic tumours, but its ability to differentiate inflammatory lesions from cancer remains unevaluated.[35]

Positron emission tomography (PET) is a relatively new imaging technique in which the increased uptake of 2(^{18}F)-fluoro-2-deoxy-D-glucose (FGF-PET) observed in malignant tumours has been used in the differential diagnosis between pancreatic cancer and chronic pancreatitis. In a series of 80 patients, Freiss *et al* reported an increased uptake in 41 of 42 (98%) patients with pancreatic cancer and four of six (67%) with peri-ampullary tumours compared with no accumulation in 28 of 32 (88%) patients with chronic pancreatitis.[36] The overall sensitivity and specificity were 94% and 88%, respectively. Inokuma *et al* correctly identified a carcinoma in 33 of 35 (94%) patients with suspected pancreatic cancer using FGF-PET compared with a correct diagnosis in 31 (89%), 31 (89%) and 28 (88%) patients using CT, transabdominal ultrasound and endoscopic ultrasound, respectively.[37] Although promising, the clinical value of FGF-PET scanning requires further evaluation.

Endoscopic retrograde cholangiopancreatography (ERCP) in conjunction with CT scanning (for evidence of diffuse calcification) are the most sensitive investigations to differentiate between a neoplasm and chronic pancreatitis. In more than 70% of cases of pancreatic cancer the duct shows a sharp cut-off, usually with post-stenotic dilatation. Tapering of the main pancreatic duct, side-branch deviation, and cavity formation are also observed but none of these features can be considered diagnostic of pancreatic cancer and a normal pancreatogram may be seen in up to 10% of patients with pancreatic cancer.[38]

Clinical assessment of available diagnostic tests

Test	*Effective at identifying*	*Limitations*
Ultrasound	duct dilatation, level of obstruction of biliary tree, abnormal portal blood flow	operator dependent, unable to detect small metastasis
CT	calcification state of major vessels, abnormalities of pancreatic parenchyma	pancreatic lesions <2 cm, liver metastasis <1 cm, small (1–2 mm) peritoneal metastasis
ERCP	ductal abnormalities, fluid/brushings for cytology	peripheral lesions not involving the major ducts
Tumour markers	elevated in most patients with carcinoma	sensitivity and specificity <90%
Endoscopic ultrasound	pancreatic tumours < 3cm in diameter, facilitates biopsy	operator dependent, unable to identify accurately lymph node metastasis or distant metastasis
Laparoscopic ultrasound	liver metastasis, peritoneal seedlings and vessel encasement	invasive procedure and operator dependent
MRI	small non-organ deforming tumours, early fibrosis in chronic pancreatitis	small (<1–2mm) peritoneal deposits, poor detection of calcification
PET	carcinoma of pancreas and small metastases	low sensitivity for ampullary tumours

Box 4

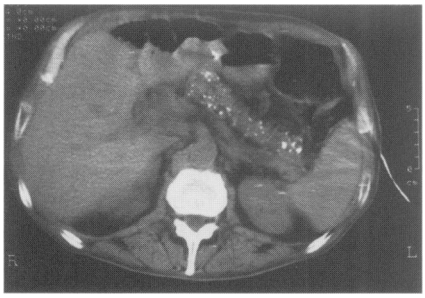

Figure 1 CT scan of the pancreas with diffuse calcification in the gland. At operation, biopsy confirmed locally advanced adenocarcinoma in the neck and body

HISTOLOGY AND SEROLOGY

Histological confirmation of the diagnosis can be attempted by percutaneous or endoscopic biopsy with a high specificity, but a relatively low sensitivity, making it difficult to exclude malignancy. Furthermore the sensitivity inevitably falls with smaller lesions which are potentially resectable.[39] A further limitation to percutaneous biopsy is concern about seeding along the biopsy tract.[40] Pre-operative biopsy of potentially resectable lesions is not therefore recommended.

Serological markers such as CA19-9 and CEA are often elevated in pancreatic cancer but moderate elevation is also encountered in inflammatory disease. Although marked serum elevation of CA 19-9 (>1000 U/ml) is highly specific, it is usually only seen in advanced unresectable tumours.[41] Measuring serum tumour markers may be helpful in selected cases, but their overall clinical applicability in differentiating between inflammatory lesions and small resectable tumours in the head of the pancreas is limited.

New diagnostic developments

Current diagnostic tools remain limited by their inability to identify small, potentially resectable tumours and restrictions in establishing the pre-operative diagnosis, because of fear of disseminating the tumour. Laparoscopic ultrasound is potentially the most sensitive method of detecting small liver metastases and may indicate vessel encasement,[42] but the fear of peritoneal seeding precludes biopsy of the primary tumour by this route. In a comparative study with dynamic CT scanning and MRI, endoscopic ultrasound was found to be the most sensitive and accurate method for diagnosing pancreatic tumours,[43] although it was not accurate for the detection of distant metastasis due to the limited penetration depth of ultrasound. The development of a biopsy port may prove to be especially useful, as the transluminal biopsy should only result in seeding in the duodenal wall, which would be resected *en bloc.*

Developments in molecular biology have also provided the potential for advances in diagnostic techniques. Mutations in codon 12 of the K-ras proto-oncogene have been identified in 70–95% of pancreatic cancers[44] and can be identified from cytological brushings or pancreatic juice taken at ERCP. The application of the polymerase chain reaction enables DNA to be successfully analysed at the nanogram level, and may increase the sensitivity of this diagnostic approach, particularly in small tumours.

Current management

Investigation of pancreatic disease is currently a multimodality process, requiring a combination of investigations. Most patients will require CT scanning with intravenous contrast, in combination with ERCP. Transabdominal ultrasound, particularly in combination with pulsed Doppler imaging, will increase the sensitivity and specificity in identifying smaller lesions. In selected cases, endoscopic and laparoscopic ultrasound will further increase the sensitivity of these tests. These investigations remain restricted in their ability to differentiate between inflammatory and neoplastic lesions, however.

Establishing a tissue diagnosis remains problematic. Percutaneous biopsy of potentially resectable lesions cannot be recommended. Unfortunately the sensitivity of brush cytology, and aspiration of pancreatic fluid is insufficient to exclude a neoplasm. In these cases the selective use of laparoscopy or endoscopic ultrasound with transduodenal biopsy may improve our ability to establish a pre-operative diagnosis. In patients in whom diagnostic uncertainty remains despite the use of all available investigations, surgical resection must be undertaken in order to establish a tissue diagnosis, since in specialist hands the

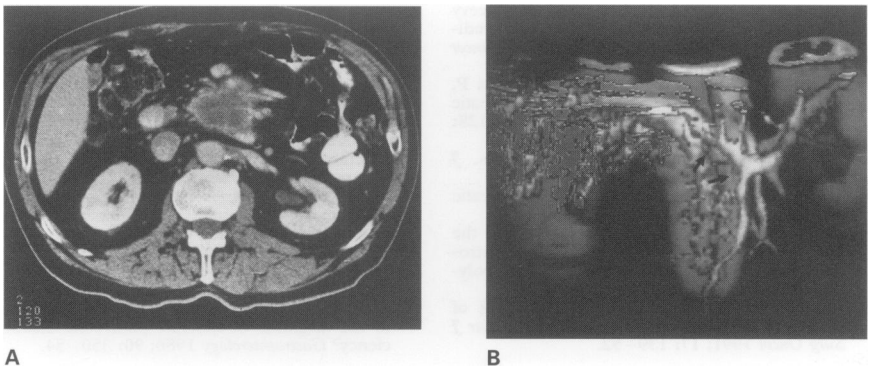

Figure 2 (A) Contrast-enhanced CT scan of an unresectable carcinoma of the head of the pancreas. (B) Three-dimensional reconstruction of the vessels, with compression of the superior mesenteric vein at the junction with the portal vein and encasement of the superior mesenteric artery

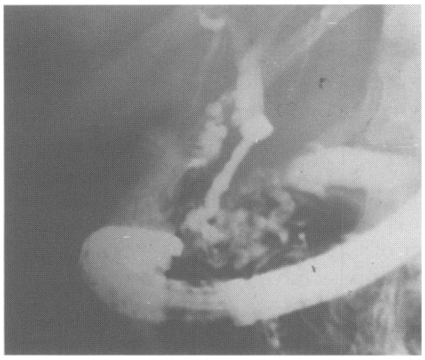

Figure 3 ERCP. Diffuse stricturing and dilatation of the main pancreatic duct is typical of chronic pancreatitis, which in this case is accompanied by a small stricture of the lower main bile duct

postoperative mortality following resection for chronic pancreatitis is now under 2%.[45] In the foreseeable future, the study of molecular markers for evidence of underlying neoplastic change is a potentially exciting diagnostic advance.

Conclusions

Pancreatic cancer and chronic pancreatitis are related in many of their aetiological and pathological features. They can also share a nonspecific clinical presentation that requires a high index of suspicion on the part of the clinician to reach the correct diagnosis. There remains a degree of reluctance in diagnosing these conditions because both are commonly perceived as incurable but this perception can now be challenged. Early diagnosis and resection of pancreatic adenocarcinoma will result in a five-year survival rate of 10–20%. Radical surgery in specialist hands can be successfully carried out with a low morbidity and a peri-operative mortality below 5%. Novel adjuvant therapy regimens may further improve this figure. Tumour types other than ductal adenocarcinoma, with a better long-term prognosis should also encourage the clinician to reach an accurate diagnosis. Finally, the association with cancer syndromes, albeit rare, makes accurate diagnosis imperative in order to institute appropriate screening measures for family members.

For patients with chronic pancreatitis, early control of the aetiological factors is an essential component of management and may limit disease progression. In selected cases, particularly if the precipitating stimulus can be removed, surgery can be successful in reducing symptoms. This may occasionally be achieved by duct decompression or drainage of a large pseudocyst. In more advanced disease, limited resection may control symptoms in over 80% of cases.[46]

All large series of pancreatic resections for carcinoma include between 5 and 10% of cases which are subsequently shown to be chronic pancreatitis (and vice-versa) indicating that further improvements in diagnosis are required.

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