## Case 29

A 50-year-old male university science lecturer presented for follow up with his gastroenterologist. He had previously had recurrent acute pancreatitis with four episodes over a period of 3 years, each with a marked increase in serum amylase. The last attack was a year ago. He denied drinking any alcohol. A cholecystectomy had been carried out after his second attack of pancreatitis. He reported some postprandial fullness and 4kg weight loss. He had no other medical history and was on no medication. Examination was normal.

### Investigations showed:

- Hb 14.0g/dL, WCC 5.6 x $10^9$/L, platelets 145 x $10^9$/L
- Na 135mmol/L, K 4.1mmol/L, urea 3.5mmol/L, creatinine 75µmol/L
- Bilirubin 15µmol/L, AST 40 IU/L, ALT 40 IU/L, ALP 60 IU/L, GGT 35 IU/L, albumin 40g/L
- Amylase normal
- CA 19.9 normal
- A CT of the abdomen carried out 2 years previously had shown a pseudocyst in the head of the pancreas. Follow-up CT of the abdomen is illustrated (Fig. 29.1 and 29.2).
- An endoscopic ultrasound (Fig. 29.3) was carried out to characterize the lesion. This showed a very large cystic dilatation of the main pancreatic duct. There were multiple papillary projections. The main pancreatic duct was grossly dilated. A 'fish-mouth' papilla was also seen (Fig. 29.4 in the central coloured section).

### Questions

29a) What are the causes of recurrent acute pancreatitis?

29b) What is the differential diagnosis of the above lesion? Describe how to differentiate between these diagnoses.

29c) How would fine-needle aspiration assist in diagnosis of this lesion?

29d) How should this patient be managed?

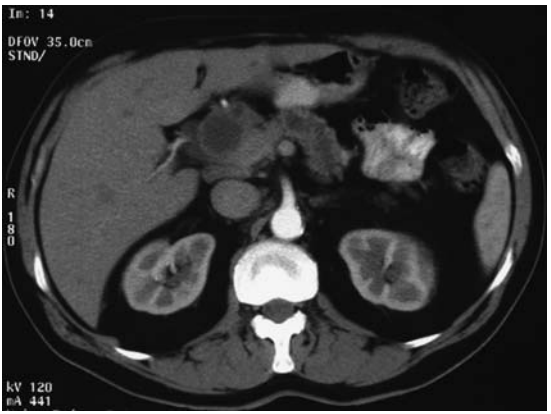


**Fig. 29.1** CT scan.

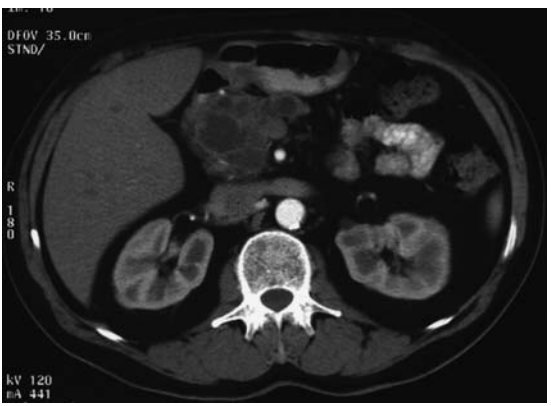


**Fig. 29.2** CT scan.

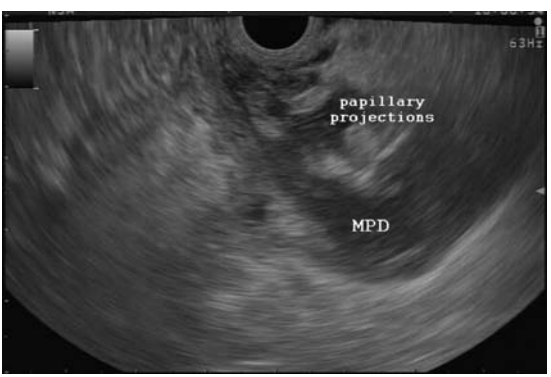


**Fig. 29.3** Endoscopic ultrasound.
MPD: main pancreatic duct

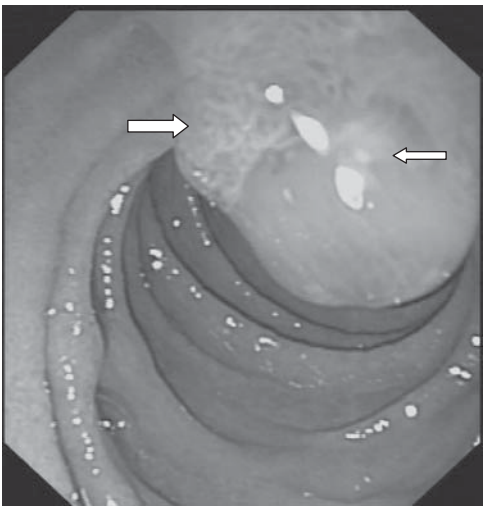

**Fig. 29.4** (see colour plate 13) Papilla at ERCP.
Mucin extruding (small arrow) from the distorted papilla (large arrow).

## Answers

29a) **What are the causes of recurrent acute pancreatitis?**

Any cause of acute pancreatitis may lead to further episodes if it is not corrected. The history and conventional diagnostic tests including blood tests for calcium and triglycerides, abdominal ultrasound to look for gallstones, MRCP, and CT scan of the abdomen, generally detect the cause of recurrent episodes of pancreatitis in 70% of cases. Endoscopic ultrasound may detect small stones in the common bile duct missed at ultrasound or MRCP. In view of the potential complications from ERCP (see Case 9), ERCP is now rarely an appropriate *diagnostic* investigation, although may be an appropriate *therapeutic* intervention.

Causes of recurrent pancreatitis are shown in Table 29.1.

29b) **What is the differential diagnosis of the above lesion? Describe how to differentiate between these diagnoses**

Based on the CT and endoscopic ultrasound findings, the main differential diagnoses in this case are:

- Pancreatic cystic neoplasm:
  - Mucin-producing tumours: intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN)
  - Serous cystadenoma (SCA)
- Inflammatory pseudocyst, secondary to previous pancreatitis
- Cystic adenocarcinoma.

Although inflammatory pseudocysts are more commonly associated with episodes of acute pancreatitis, it is important to exclude non-inflammatory cystic lesions that can cause acute pancreatitis, because they can have a risk of malignant transformation.

This lesion is most likely to be **intraductal papillary mucinous neoplasm** (IPMN). IPMN is a cystic neoplasm arising from the pancreatic duct, with mucin-producing epithelium. The CT scan and endoscopic ultrasound (Figs 29.1–29.3) show that the main pancreatic duct is markedly dilated and has papillary-type projections. Solid nodules in the wall of the pancreatic duct and the 'bright' sonographic features of mucin were seen. A 'fish-mouth' papilla, with mucin extruding from the ductal orifice, is characteristic of intraductal papillary mucinous neoplasm (Fig. 29.4). These lesions have a high risk of malignant transformation and can present with acute pancreatitis that is often recurrent. They are commonly **misdiagnosed** as the far more common 'pseudocysts'.

**Table 29.1** Causes of recurrent pancreatitis

| | |
|---|---|
| **Mechanical** | |
| | **Congenital**<br>Pancreatic divisum, annular pancreas<br>**Acquired**<br>• Gallstones (most frequent aetiological factor)<br>  • Microlithiasis (<2mm in diameter and usually seen at endoscopic ultrasound and ERCP)<br>  • Gallbladder sludge (usually seen on ultrasound)<br>  • Common bile duct macrolithiasis<br>• Sphincter of Oddi dysfunction (third most common cause of recurrent acute pancreatitis after gallstones and alcohol<br>• Benign and malignant tumours of the pancreatic ductal systems<br>• Strictures of the pancreatic duct<br>• Choledochocele |
| **Toxic** | |
| | • Alcohol (very common cause)<br>• Organophosphates |
| **Drug-induced (dose-dependent or idiosyncratic reactions)** | |
| | • Examples – azathioprine, oestrogens, metronidazole, corticosteroids |
| **Metabolic** | |
| | • Hypertryglyceridaemia<br>• Hypercalcaemia |
| **Familial and inherited** | |
| | • Cystic fibrosis transmembrane regulator (CFTR) gene mutation<br>• Trypsinogen gene mutation |
| **Miscellaneous** | |
| | • Vasculitis<br>• Viral (mumps coxsackie) or parasitic infection<br>• Tuberculosis |
| **Idiopathic (<10% of cases if investigated in detail)** | |

As for differentiating an intraductal papillary mucinous neoplasm from other pancreatic cysts, Table 29.2 summarizes the characteristics of four common cystic lesions. A post-inflammatory pseudocyst is by far the most common.

29c) **How would fine-needle aspiration assist in the diagnosis of this lesion?**

Endoscopic ultrasound-guided, fine-needle aspiration yields fluid for cytology and chemical analysis. **Cytology** can be obtained in up to 80% of pancreatic cystic lesions (Table 29.2). **Cyst fluid** should be analysed for amylase (indicating communication with the pancreatic duct), and tumour markers such as CEA. Interpretation remains difficult and specialist advice is appropriate. A prospective study of 112 cysts reported a CEA <5ng/mL

**Table 29.2** Differentiating pancreatic cystic lesions

| Clinical | Morphology | Cystic fluid | Cytology | Malignant potential |
|---|---|---|---|---|
| **Intraductal papillary mucinous neoplasm** | | | | |
| Equal gender distribution<br>6–7th decade<br>Recurrent pancreatitis or abdominal pain occasionally found | Macrocyctic-and microcystic with dilatation of pancreatic duct | Viscous, transparent, with mucin | Mucinous columnar cells with atypia<br>Fluid stains positive for mucin | Yes |
| **Mucinous adenocarcinoma** | | | | |
| Females in 5th decade, especially from Asia,<br>Often coincidentally detected, but can cause pain if large | Macrocystic or septated, may have thickened walls<br>Peripheral calcification, with a solid component,<br>No communication with pancreatic duct | Viscous, transparent, with mucin | Unique ovarian- like stroma | Yes |
| **Serous cystadenoma** | | | | |
| Females in 7th decade | Microcystic or honeycomb lesion<br>20% are macrocystic | Thin, non-mucinous, haemorrhagic | Monomorphic cuboidal cells with clear, PAS-positive cytoplasm | No |
| **Post-inflammatory pseudocyst** | | | | |
| History of acute pancreatitis | Unilocular, thick walled<br>Septations are unusual | Glutinous, dark and opaque | Inflammatory cells, without mucin or epithelial cells | No |

consistent with a serous cystadenoma, but when >192ng/mL indicated a mucinous adenocarcinoma (sensitivity 75%, specificity 85%). No other tumour markers (including CA 19.9) are accurate enough to provide a definitive diagnosis. When morphological criteria, cytology, and CEA >192ng/mL were combined, endoscopic ultrasound could differentiate mucinous from serous lesions with 91% sensitivity and 31% specificity.

The aspirate of this lesion had a high amylase resulting from communication with the pancreatic duct. Cytology showed columnar cells with atypia, and a CEA of 230ng/mL. This was consistent with an intraductal papillary mucinous neoplasm.

29d) **How should this patient be managed?**

**Main duct mucin-producing tumours** should, in general, be considered for resection. Endoscopic ultrasound helps predict potential malignancy on the basis of cyst wall thickness, intramural nodules, cystic dilatation of the main pancreatic duct and intracystic compartments >10mm. Intraductal papillary mucinous neoplasms are often multifocal, with a recurrence rate of 10% after surgery. Surveillance by ultrasound or MRCP may be appropriate and should be discussed with the patient. This is in contrast to mucinous cystic neoplasms, which do not recur after resection.

Before surgery, it is important to consider:

- symptoms
- age and life expectancy
- degree of surgical risk
- location and size of lesion.

Current mortality for patients undergoing pancreaticoduodenectomy is <2% in established centres. Specialist advice is appropriate.

This patient underwent a pancreaticoduodenectomy (Whipple's procedure). Histopathology confirmed an intraductal papillary mucinous carcinoma. The common bile duct and main pancreatic duct were free of tumour at the resection margin.

## Further reading

AGSE guideline (2005). the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. *Gastrointest Endosc*; **61**: 363–70.

Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL (2004). Cystic neoplasms of the pancreas. *N Engl J Med*; **351**: 1218–26.

Brugge WR, Lewandrowski, Lee-Lewandroxski E *et al.* (2004). The diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst (CPC) study. *Gastroenterology*; **126**: 1330–6.

Tanaka M, Chari S, Adsay V *et al.* (2006). International consensus guidelines for management of intraductal paillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*; **6**: 17–32.