Pancreatic pathology for the surgeon

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Abstract

The pancreas can show a wide range of pathologies that span non-neoplastic (congenital abnormalities, inflammatory and infective) to neoplastic both primary and secondary. The purpose of this article is to provide an overview of pancreatic pathology for the non-pathologist reader, particularly highlighting the commoner entities. The article also shows the importance of sampling of certain lesions in total to exclude evidence of invasion in pre-cancerous pancreatic lesions. The reader is thus provided with some insight into the detailed gross and microscopic examination involved in the assessment of many pancreatic lesions.

Keywords Neuroendocrine tumours; pancreas; pancreatic cancer; pancreatic cystic lesions; pancreatitis; pathology

Introduction

The pancreas, by virtue of its anatomical location, tends to manifest pathology late in the course of disease. However, more sophisticated imaging and awareness of pancreatic disease has resulted in pancreatic disease being diagnosed earlier. The purpose of this overview is to provide a framework with sufficient information that will enable a good working knowledge of the commonly encountered lesions in the pancreas. It is not intended to be a comprehensive, in-depth coverage of all pathological entities; for that, the reader is directed to specific published articles and specialized reference textbooks.

Non-neoplastic lesions of the pancreas

Pseudocysts

Clinical: pseudocysts account for 75%–80% of pancreatic cystic lesions, making them the most common type of cystic lesions of the pancreas.[1,2] They usually develop in the setting of severe acute pancreatitis, often in association with alcoholic pancreatitis, biliary disease, or trauma.[2] Clinically, they may cause abdominal pain, and can lead to obstruction, infection, haemorrhage or rupture. Pseudocysts are usually seen on CT as a round cystic cavity filled with fluid, surrounded by a thick wall, adjacent to the pancreas.[1]

Pathology: grossly, they present as extra-pancreatic cysts filled with haemorrhagic and necrotic material with an inflammatory attachment to the pancreas. On histology, they lack an epithelial lining and are often composed of an inner layer of inflammatory tissue, surrounded by layer of dense collagen-rich connective tissue.[1,2]

Other non-neoplastic cysts: parasitic, retention and congenital cysts

Other non-neoplastic cysts may occur in the pancreas. Parasitic cysts are rare and are usually hydatid cysts (echinococcus).[2] The diagnosis is challenging and hydatid cysts are often misdiagnosed preoperatively as cystadenoma or cystadenocarcinoma.[3] The patient may present with pancreatitis secondary to main pancreatic duct obstruction. On imaging, multiple subcysts and calcifications may be seen.[3] Avoiding perioperative cyst rupture, which can lead to abdominal echinococcosis implantation is crucial.

Retention cysts occur in the pancreatic duct as a consequence of obstruction and are usually small (<1 cm), well defined and unilocular.[2,4] In contrast, congenital cysts do not communicate with the duct system, they are intrapancreatic and lined by cuboidal epithelial cells.[2,4] Multiple congenital cysts may be seen in association with von Hippel–Lindau disease or inherited polycystic kidney disease.[2]

Rarely, benign cystic entities such as lymphangioma, endometriosis, and lymphoepithelial cyst may also involve the pancreas.[1]

Chronic pancreatitis

Chronic pancreatitis (CP) can be grouped into three different categories based on aetiology: (i) alcoholic pancreatitis; (ii) obstructive pancreatitis; and (iii) hereditary pancreatitis.[5] CP of any type can cause scarring of the pancreas and mimic malignancy.[1,5]

Incidence: the incidence of CP in Western countries is about 10 cases per 100,000, with a prevalence of up to 40 cases per 100,000 subjects.[5]

Clinical: CP commonly presents with recurrent episodes of abdominal pain, which decrease in incidence and severity over time with progressive destruction of the glandular parenchyma, leading ultimately to endocrine and exocrine failure.[5]

Pathology: the macroscopic features of CP vary with the stage and underlying aetiology of disease. Similarly, the histology may vary; however; the most common features are represented by the triad of fibrosis, loss of acini and duct changes.[6]

Autoimmune pancreatitis (types 1 and 2)

Clinical: autoimmune pancreatitis (AIP) is a type of chronic pancreatitis noted for causing mass-like lesions within the head of the pancreas which may be difficult to distinguish from carcinoma clinically and radiologically.[1] Less commonly, AIP may present as lesions in the body, tail, or cause diffuse 'sausage-like' enlargement of the pancreas.[1,7] AIP may mimic adenocarcinoma by causing stenosis of the bile duct, leading to jaundice, as well as elevated serum carcinoembryonic antigen (CEA) and carbohydrate antigens (CA) 19-9 and DUPAN-2.[1] Serum IgG4 level is elevated in up to 80% of type 1 AIP cases and can be helpful to distinguish type 1 AIP from adenocarcinoma.[1,8] Recognizing AIP preoperatively avoids pancreatectomy, as the disease responds to biliary drainage and steroid therapy.[1]

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Pathology: there are two types of AIP, which are macroscopically indistinguishable and can appear as milky-white to yellowish sclerotic pseudo-tumours on gross examination.[1] Type 1 AIP is part of a systemic autoimmune immunoglobulin (Ig) G4-related disease and typically affects men >60 years, whereas type 2 AIP is more pancreas specific, shows no gender predilection and affects patients in their 4th-5th decades.[5] Microscopically, type 1 AIP consists of an inflammatory infiltrate composed of T lymphocytes and plasma cells centered around medium to large interlobular ducts with periductal fibrosis and marked venulitis affecting small to medium sized veins.[1,5] Perineural inflammation and lymphoid aggregates are also commonly seen. Inflammation may extend to the surrounding parenchyma in later stage disease and fibrotic changes may assume a whorled or storiform pattern.[5] IgG4 immunostain is helpful in the diagnosis. The thresholds of >10 IgG4 positive plasma cells per high power field (HPF) on biopsy and >50 IgG4 positive plasma cells per HPF on resection are helpful.[9] The overall proportion of IgG4:IgG ratio of plasma cells is typically 40%.[5,9]

In type 2 AIP, 'granulocytic epithelial lesions' (GEL) characterized by invasion and destruction of ductal epithelium by neutrophils and eosinophils are seen affecting small- and medium-sized ducts.[1] Similar to type 1 AIP, periductal lymphoplasmacytic inflammation is seen. Acinar atrophy and periductal fibrosis may also be seen but are typically less pronounced in comparison to type 1 AIP.[5]

Groove/paraduodenal pancreatitis

Clinical: paraduodenal/groove pancreatitis (PGP) is another type of chronic pancreatitis which may present as a mass and present with features worrisome for carcinoma of the pancreatic head.[1] It occurs predominantly around the duodenal wall near the minor papilla, often involving the 'groove area', an anatomic region between the pancreatic head, duodenum, and common bile duct.[5] The majority of patients with PGP are men in their 5th decade, with a history of smoking and alcohol abuse.[10] The pathogenesis has not been fully elucidated; however, chronic obstruction of the minor papilla is thought to lead to the common clinical syndrome of upper abdominal pain, postprandial vomiting and weight loss due to duodenal stenosis.[1,5] CT often reveals a thickened duodenal wall with associated hypodense mass in the groove or cystic changes.[1]

Pathology: macroscopic appearance of the cut section shows the epicenter of PGP to be around the minor papilla with variable extension to the groove.[5] The lesion may appear gelatinous to whitish and firm, or cystic and filled with proteinaceous debris.[1,5] Often, the duodenal mucosa acquires a cobblestone appearance and the duodenal wall and underlying pancreatic parenchyma are thickened and fibrotic.[5] The terminal common bile duct may be narrowed.[1] Lymphadenopathy may be macroscopically evident in PGP.[5] On microscopy, there is dense fibrosis of the duodenal wall around the minor papilla which may extend to the groove area and pancreatic parenchyma with associated Brunner gland hyperplasia.[1,5] The cystic region usually includes multiple cysts lined by ductal epithelium, which may contain small calculi.[5] Late-stage disease may show atrophy of the pancreas, chronic inflammation, fat necrosis, fibrosis, and prominent nerve bundles.[5]

Treatment: therapeutic strategy can be supportive. However, due to the presentation and differential diagnosis of malignancy, pancreatoduodenectomy may be indicated if symptoms are severe and conservative management fails.[1,5]

Intrapancreatic accessory spleen (IPAS)

Prevalence: accessory spleen is a common entity, identified in up to 30% of individuals at autopsy.[1]

Clinical: the most common location for accessory spleen is in the splenic hilum followed by the pancreatic tail.[1,11] IPASs are often found incidentally on imaging in patients 50–70 years of age, as well-circumscribed lesions, usually <2 cm in diameter.[1] Due to their location and their hypervascular and homogeneous appearance on imaging, IPASs may mimic a hypervascular pancreatic neuroendocrine tumour (PanNET).[1,5,11] Diagnosis can sometimes be made on EUS-FNA, which may help prevent an unwarranted surgery; however, a subtle lesion in the tail of the pancreas will usually be resected to avoid missing a tumour.[1]

Pathology: grossly, IPASs are circumscribed brownish nodules surrounded by normal pancreas.[1,5] On histology (Figure 1), the nodule is composed of mature splenic tissue with a normal distribution of white pulp (lymphoid tissue) and red pulp (connective tissue with vessels).[5]

Pancreatic hamartoma

Clinical: pancreatic hamartomas are defined as a benign overgrowth of cells, and considered to be a malformation rather than a neoplasm. These rare lesions can be solid and/or cystic, are usually located in the head of the pancreas, and mimic malignant tumour.[5,12]

Pathology and treatment: on histology, pancreatic hamartomas are composed of three components in varying amounts: small ductal structures, fibrous stroma and disorganized acinar parenchyma.[5]

The biological behaviour is benign; however, pancreatic hamartomas typically require surgical resection due to the differential diagnosis of malignant tumour preoperatively.[5,12]

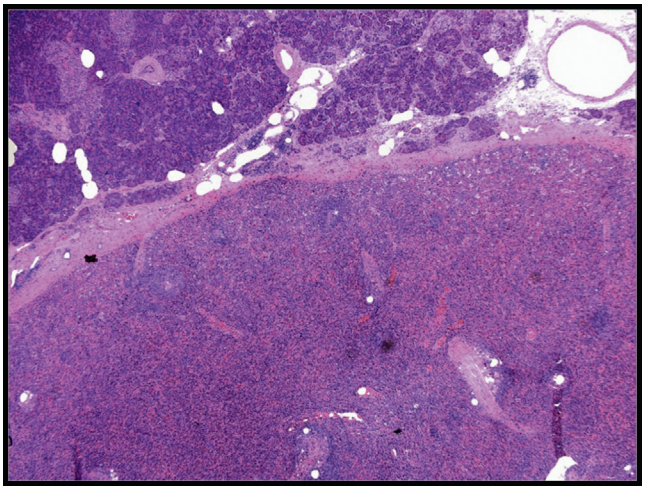

Figure 1 Intrapancreatic accessory spleen. Within the pancreatic parenchyma normal spleen can be seen.

Neoplastic lesions of the pancreas

Secondary or metastatic tumours

The pancreas can be the metastatic site of any tumour be it of epithelial (carcinoma), connective tissue (sarcoma) or haematopoietic (leukaemia/lymphoma) or melanocytic origin. Thus, consideration of lung cancer, breast cancer, renal cell carcinoma, malignant melanoma, carcinoma of gastrointestinal origin and prostate cancer metastatic to the pancreas should always be considered before immediately assuming that a tumour is a primary pancreatic one.

Primary pancreatic neoplasms

Pancreatic ductal adenocarcinoma

Incidence: this is the most common primary pancreatic tumour and in some series accounts for up to 85%–90% of all pancreatic tumours.[13]

There are well-recognized associations and/or conditions that predispose to the development of pancreatic adenocarcinoma. These include: cigarette smoking, obesity, alcohol abuse, chronic pancreatitis, solid organ transplantation, diabetes and primary pancreatic tumours such mucinous cystic neoplasm and intraducutal papillary mucinous neoplasms.

There is also an increasingly recognized hereditary or genetic input with familial pancreatic cancer, mutations of *BRCA-1* and *2*, Lynch syndrome, familial atypical multiple mole melanoma (FAMMM), Peutz–Jeghers syndrome and hereditary pancreatitis, all thought to potentially increase the risk of development of pancreatic ductal adenocarcinoma.

Clinical: it was typically considered a disease of the elderly; however, younger patients are now encountered increasingly, and the age range is from 60 to 80 years, although cases in the under 60 age group are seen. It is important to remember that pancreatic cancer is no longer a disease restricted to the very elderly and should always be considered in a clinical differential diagnosis. Symptomatology is usually late but unexplained weight loss, back pain and finally obstructive jaundice are typical. Rarely, patients can produce evidence of distant thrombosis. Often times, patients present with evidence of metastatic disease which attests to the aggressive nature of pancreatic cancer.

Pathology: 65%–70% of pancreatic adenocarcinomas occur in the head of pancreas.

Macroscopically, pancreatic ductal cancers are infiltrative and invasive hence do not form a discrete tumour mass (Figure 2). As a consequence of the invasive growth characteristics, the pancreatic stroma responds by becoming firm, fibrotic and desmoplastic allowing for distinction from normal pancreas.

Microscopically, it is an adenocarcinoma that recapitulates normal pancreatic ductular tissue if well differentiated and is made up of glandular or duct-like structures, lined by atypical cells manifesting cytoplasmic clearing, enlarged irregular hyperchromatic nuclei, displaying a haphazard invasive growth pattern eliciting stromal desmoplasia (Figure 2). Typically, pancreatic adenocarcinoma shows perineural invasion and can be widely invasive into peripancreatic tissue, ampulla of Vater, common bile duct, duodenum.

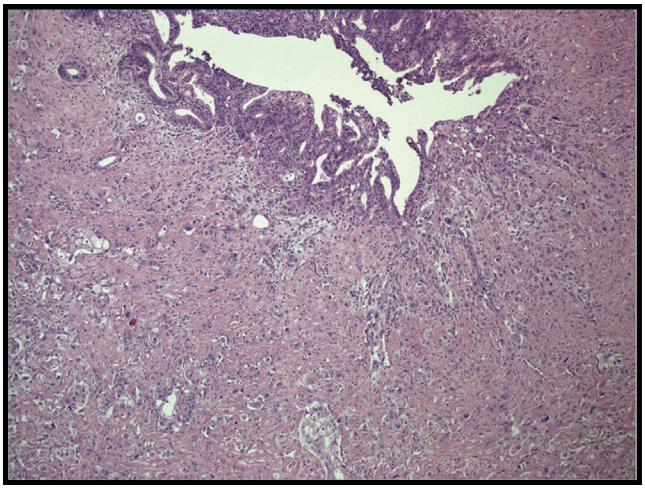

Figure 2 Infiltrating single cells and occasional ductular structures with a fibrotic stromal response in keeping with an invasive pancreatic ductal adenocarcinoma.

Treatment and outcome: in general, the outcome for pancreatic cancer is poor and only 20% of cases are amenable to be resected at the time of presentation.[14] The advent of neoadjuvant treatment such as FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil and leucovorin), has become a therapeutic option for locally advanced cases with the hope of downstaging borderline resectable tumours, and this has improved survival rates in patients who then go on to have resections.

The impact of neoadjuvant treatment has impacted on the handling and processing of the pancreatic resection specimens in terms of tumour identification and grading of regression changes seen microscopically. In many institutions the entire pancreas is sampled and mapped to correlate with imaging. Pathologists then produce a regression score which can impact on survival data.

Intraductal papillary-mucinous neoplasm (IPMN)

Initially described as a 'mucin-producing pancreatic adenocarcinoma associated with a favourable prognosis', several appellations were applied to this very characteristic pancreatic lesion: atypical papillary hyperplasia, intraductal papilloma, papillary adenoma, villous adenoma, diffuse villous carcinoma of the duct of Wirsung, villous adenoma of the main pancreatic duct, intraductal cystadenocarcinoma, cystic adenocarcinoma, carcinoma in situ, early pancreatic carcinoma, diffuse papillomatosis, diffuse intraductal papillary adenocarcinoma, multiple primitive endoluminal tumours of the main pancreatic duct, intraductal mucin hyper-secreting neoplasm/tumour, duct ectatic type pancreatic ductal carcinoma, mucinous ductal ectasia, mucinous pancreatic duct ectasia, mucin producing tumour of the pancreas and intraductal papillary neoplasm.

The accepted terminology now is 'intraductal papillary mucinous neoplasm (IPMN)'.

Definition: this is a grossly visible, non-invasive, mucin-producing, predominantly papillary, or rarely flat, epithelial neoplasm arising from the main pancreatic duct or branch ducts, with varying degrees of duct dilatation. IPMN usually produce a lesion >1 cm in diameter and include a variety of cell types with a spectrum of cytological and architectural atypia.

Incidence: IPMN are estimated to account for about 5% of pancreatic neoplasms; however, they are being reported in increasing numbers and may be more common than previously recognized.

Clinical features: clinically, patients with an IPMN usually present in the 7th–8th decade of life with non-specific abdominal symptoms, although in some, a history of pancreatitis is noted. Approximately 30% of the patients have tumours in other organs, some synchronous and others metachronous.

Pathology: IPMN is usually located in the head, body or tail of the pancreas; however, there is a predilection for the head.[15] IPMN are characterized by cystic dilatation of pancreatic ducts in which an intraductal proliferation of neoplastic mucin-producing cells is usually arranged in papillary patterns. The papillae may range from microscopic to large nodular masses. Mucin production by the neoplastic cells is usually associated with intraluminal mucin secretion, which leads to cystic dilatation of the ducts, and at times, to mucin extrusion from the ampulla of Vater, a finding that is virtually diagnostic of an IPMN. Depending on the location of the primary process and subsequent mechanical changes in the ducts, IPMN may present as a spectrum of multilocular cystic masses, villous/papillary nodules or with mucin extrusion from the ampulla.

Gross specimen: careful examination and sampling of the specimen for an invasive carcinoma component is of vital importance.

Macroscopically, two main types can be distinguished: a ductectatic mucin-hypersecreting variant in which the dilated main duct or branch ducts are filled with tenacious mucin and the lining of the cysts is flat and smooth, and a papillary-villous variant, characterized by nodular, papillary soft and friable proliferations associated with mucous material within the dilated pancreatic duct. These polypoid proliferations, along with the presence of mucin plugs, are responsible for the typical filling defects seen at ERCP. IPMN can be further separated into main-duct and branch ducts types. The main-duct type involves the main duct either in a diffuse or segmental manner. The great majority of cases arise in the main pancreatic duct of the head of the pancreas and progress along the same duct with frequent involvement of the branch ducts. The extension of the IPMN to the major and/or minor papilla creates the typical protrusion into the duodenum that can be seen either at endoscopy or on ultrasound and CT.

Microscopic examination shows papillae with three distinct morphologic patterns may be seen:

- Intestinal, which is morphologically similar to that of colonic villous adenomas of the colon (Figure 3).
- Pancreaticobiliary, in which the papillae are more complex, more slender and are lined by cuboidal cells sometimes with prominent nucleoli.
- Gastric: rarely some papillae have a gastric foveolar appearance. Since this phenotype is also common in the non-papillary areas of these tumours, it is also referred to as 'null' type.

Microscopically, the cystically dilated ducts of IPMN contain mucin-producing cells with varying degrees of atypia (low and high grade).

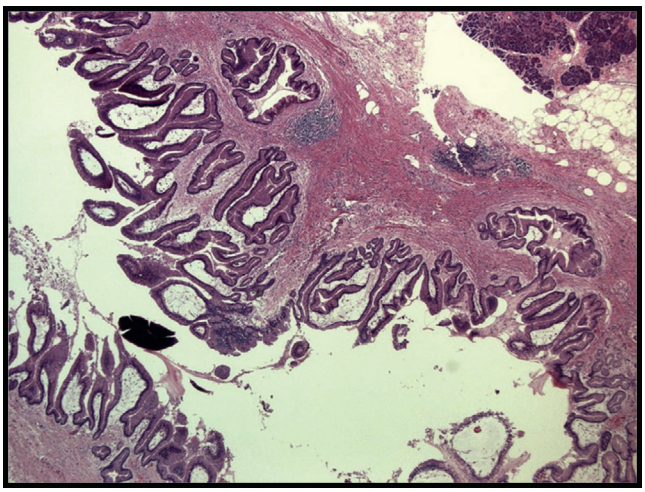

Figure 3 An example of an IPMN showing intestinal epithelium which has papillary configurations with excessive mucin production causing main pancreatic duct dilatation.

Due to the great variability within a tumour, it is important to emphasize the necessity of extensive tumour sampling to ensure the correct diagnosis and assess the presence of tumour invasion, placing special emphasis on papillary proliferations, nodular areas and sclerotic areas.

The presence of carcinomatous stromal invasion categorizes carcinomas arising from IPMN.

IPMN carcinoma is frequently characterized by the presence of mucin-filled cystic spaces, partially lined by atypical cells and containing floating mucus-secreting cells and nuclei, so-called colloid carcinoma. The overwhelming majority of colloid carcinomas in the pancreas arise from preexisting IPMN. The finding of a colloid carcinoma in the pancreas should prompt the pathologist to search for an IPMN. The presence of a glandular component that characterizes the 'glandular' pattern (like the usual ductal pancreatic carcinoma) is less frequently encountered with IPMN.

Radiology: when the size of the main pancreatic duct is found to be more than 5 mm in diameter on CT scanning and more than 4 mm on ultrasonography, then the duct is judged to be dilated. Dilatation of the main pancreatic duct is much more than dilatation of branch ducts. These dilatations may appear as clusters of small cysts or as filling defects. Filling defects tend to be more prevalent in the main duct IPMN. The diagnostic accuracy rate of the preoperative tumour imaging for histologically proven lesions is approximately 80% in the main duct group and 95% in the branch duct IPMN. Main pancreatic duct diameter equal to or greater than 15 mm (for main duct and combined duct types) and size of the cystic tumour equal to or greater than 30 mm (for branch duct type), show a high prevalence of adenocarcinoma. A threshold value of 15 mm for the main pancreatic duct shows 70% of tumours less than 15 mm were benign, whereas 87% of those with a diameter of 15 mm or more were malignant. In the case of branch duct type tumours, 90% larger than 30 mm were malignant while 30% of tumours smaller than 30 mm did not contain invasive carcinoma. Tumours with mural nodules have a significantly higher incidence of carcinoma. Endoscopic ultrasonography and magnetic resonance cholangiopancreatography are

better than endoscopic retrograde cholangiopancreatography (ERCP) for the setting the location of the tumour and the presence of mural nodules. Typical ERCP findings include: swelling of the papilla/ampulla of Vater, dilatation of the orifice of the papilla or mucin secretion from the orifice. Filling defects of the pancreatic duct system are also noted.

Treatment and behaviour: surgery is the best therapeutic option and guidelines or indications for surgery and an algorithm have been recommended.[15,16]

Intraductal oncocytic papillary neoplasm (IOPN): this subtype is regarded a special subtype of intraductal papillary mucinous neoplasm, and recent molecular findings suggest that it may be different from other types of IPMN. Grossly, these neoplasms exhibit cystic dilatation of the pancreatic ducts, many of which contain large, tan and friable nodular proliferations. The neoplasms are relatively large (mean size: 5.2 cm) at the time of diagnosis. The papillae of IOPN exhibit a 'pancreaticobiliary (PB)' pattern (also called compact cell type), which is characterized by exuberant, arborizing papillae lined by one to five cell layers of cuboidal cells. The nuclei in IOPN contain single, prominent and eccentric nucleoli. The cells of IOPN are oncocytic, due to an abundance of mitochondria and the paucity of other organelles, which is reflected histologically as abundant, granular, acidophilic cytoplasm. In most cases, the degree of cytoarchitectural atypia, the exuberance of the papillae and the presence of mitoses qualify for the diagnosis of at least carcinoma in situ.

Preliminary molecular analyses have shown that IOPN may differ from the conventional IPMN by the lack of *KRAS* gene mutations and alternate MUC phenotypes.

The data on the clinical course of IOPN is limited; however, it seems to be similar to that of typical intraductal papillary mucinous neoplasms, but may be even more indolent.

In addition to mucinous carcinomas of the pancreas, the following have been associated with IPMN: it has been encountered in FAP and AFAP patients, gastric, colon, oesophageal and lung cancer.

Solid pseudopapillary tumour of pancreas (SPT)

This tumour was first described in 1959 by Virginia Frantz and is also known as the Gruber–Frantz tumour. The tumour has been called by several related names: solid and papillary epithelial neoplasm, papillary and solid epithelial neoplasm, papillary cystic and solid tumour, papillary cystic tumour and solid pseudo-papillary tumour, which is the preferred term.[17]

Incidence: this is an uncommon, low-grade malignant neoplasm accounting for approximately 1% of all exocrine pancreatic tumours. The histogenesis is uncertain with acinar, ductal, endocrine and primordial cell origin all being proposed.

Clinical features: SPTs tend to occur in young patients, although the age range is wide: 2–81 years of age; 90% occur in females. Symptoms are non-specific with nausea, vomiting, abdominal fullness, abdominal pain and an abdominal mass all being described. Often it is an incidental finding detected as a calcified mass on abdominal X-ray. Imaging shows a well-circumscribed mass which is hypodense and often cystic.

Pathology: these tumours occur in the tail, then the head and, least commonly, the body of the pancreas. They vary in size from 1.5 up to 30 cm with an average of 10.5 cm. They have a well-demarcated, smooth external surface with delicate bosselations. On cut section there are areas of necrosis, haemorrhage, cystic degeneration and solid areas. The tumours appear red to tan in colour. They tend to produce a single tumour mass and multicentric cases are extremely rare.

Microscopically, the solid areas have a rich endocrine type of vascular pattern. The individual tumour cells are relatively uniform, cuboidal to polygonal in shape with eosinophilic to clear cytoplasm; hyaline globules are frequently noted within the cytoplasm. The nuclei are round to oval with the delicate chromatin and often contain longitudinal nuclear grooves. Sometimes there is nuclear irregularity manifest by indentations of the nu- clear membrane and nuclear pseudo-inclusions. Mitoses are rare, although there may be necrosis and degeneration. A typical feature is the presence of foamy tumour cells, which should not be confused with foamy macrophages, which also occur in this tumour. The pseudopapillary pattern results from dyscohesion of tumour cells and the residual viable cells cling to vascularized stroma (Figure 4). Hence, these are not true papillary structures. Areas of fibrosis, fresh and old haemorrhage, foamy macro- phages, cholesterol clefts, granulomas, hyalinization, calcification and even ossification can be seen.

Behaviour: Up to 85% of SPTs are benign. Metastasis occurs in 10%–15% at the time of presentation and occurs in the peritoneum or liver. Lymph node metastases are rare. Complete surgical resection is the preferred mode of treatment.

E-cadherin and b-catenin are important molecules in the wnt signalling pathway and both have been shown recently to be of diagnostic value in SPT. The reason these two proteins warrant separation from all the other markers is that they yield consistent results in 100% of cases of SPT. It is for this reason that they are now regarded as two of the pre-eminent antibodies in the routine panel used to investigate SPT.

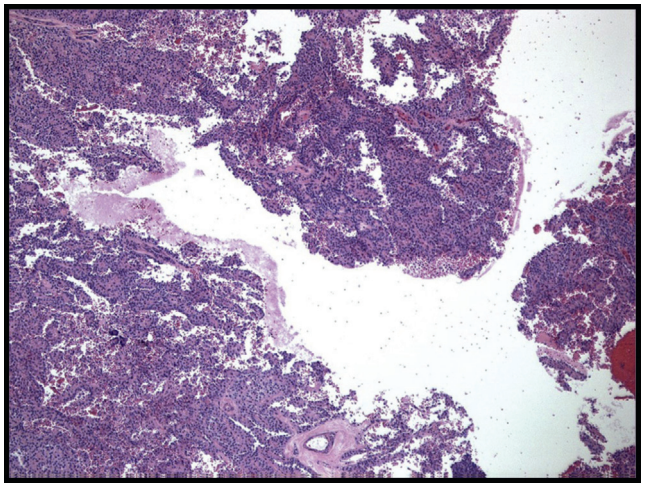

Figure 4 Solid papillary neoplasm is characterized by degeneration, haemorrhage, cystic change and pseudopapillary structures resulting from loss of cell cohesion.

Serous microcystic adenoma

Primary pancreatic cystic neoplasms (PCNs) are rare.[18] However, cystic tumours of the pancreas have become an increasingly prevalent and diagnosed entity, most likely due to the improvement in radiological diagnostic techniques.

Incidence: serous cystic neoplasms (SCNs) account for about 25% of all pancreatic cystic tumours and comprise 1%−2% of all exocrine pancreatic neoplasms.[4]

Clinical features: serous cystic neoplasms occur in adults and the elderly, and affect females twice as frequently as males. Most patients are asymptomatic, but if symptomatic, clinical features may include nausea, vomiting, weight loss, abdominal or epigastric pain, diarrhoea and a palpable abdominal mass. Less common clinical features, mostly acute complications of the neoplastic lesion, include: obstructive jaundice, recurrent pancreatitis, acute gastrointestinal haemorrhage due to duodenal ulceration by the tumour, and haematoperitoneum and peritonitis secondary to rupture of the tumour or erosion of intramural or peritumoral vessels. Rarely, portal hypertension secondary to splenic vein occlusion by the tumour, and Evan's syndrome (coexisting immune destruction of red blood cells and platelets) can occur.

Von Hippel−Lindau disease (VHL) is a heritable, autosomal dominant, multisystem cancer syndrome with high penetrance, that is associated with a germline mutation of the *VHL* tumour suppressor gene on the short arm of chromosome 3. The disease is characterized by the presence of benign and malignant tumours, primarily retinal capillary haemangioma, and haemangioblastomas of the cerebellum and spinal cord. Other associations include renal cell carcinoma, phaeochromocytomas, epididymal cystadenomas, endolymphatic sac tumours, and benign cystic lesions of the lung, liver, spleen, adrenal, kidney, and pancreas. Pancreatic involvement is common and occurs in 60%−80% of patients with VHL disease, and SCAs are the most common manifestation of pancreatic disease, occurring in 35% −75% of VHL patients. Rarely, cases of SCA associated with pancreatic divisum have been reported.

Radiology: preoperative imaging studies include computed tomography (CT) scan, endoscopic ultrasonography (EUS), endoscopy retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography. CT scan and EUS are ideal imaging tools in diagnosing pancreatic cystic lesions, but because of the variability in the morphological appearance of pancreatic SCNs, and overlapping features with other pancreatic lesions, misdiagnosis by CT scan or EUS occurs in 25%−50% of cases thus requiring ancillary studies for a definitive diagnosis. MRI has a diagnostic accuracy of 74%.

Radiological studies demonstrate three distinct patterns:

- A polycystic pattern (70% of cases), which is characterized by a bosselated collection of cysts that range in size from a few millimetres to 3 cm.
- A honeycomb pattern (30% of cases), in which the tumour consists of numerous small microlacunae separated by thin fibrous septa.
- Macrocystic pattern (10% of cases), which is characterized by the presence of a well-circumscribed, encapsulated, sometimes ill-defined mass, composed of few (oligolocular) macrocysts (1.5−4.5 cm in diameter), or containing only a single macrocyst (unilocular).

Less commonly, SMAs may have a homogeneous, solid appearance on imaging due to haemorrhage into the cystic spaces. A characteristic, pathognomonic stellate, sunburst pattern of calcification within a central fibrous scar is present in 10%−30% of cases. Arteriography can demonstrate the hypervascular nature of SCNs. Except in rare cases, SCNs lack communication with the pancreatic ductal system.

Pathology: serous cystadenomas occur in the head and tail of the pancreas in equal frequency and less commonly in the body. They range in size from less than 1 cm up to 30 cm. The tumours are generally solitary, rounded, lobulated and well-demarcated. Uncommonly, SCAs may present as multiple synchronous tumours, which may exhibit a confluent growth pattern and diffusely involve the pancreas. There is no gross communication between the SCAs and pancreatic duct system. Serous microcystic adenomas are characterized by a honeycomb appearance, and are composed of numerous small microcysts or, to a lesser extent, larger cysts (>1−2 cm), separated by thin fibrous septa and filled with serous fluid. A central stellate fibrous scar with areas of calcification and focal haemorrhage are usually present. The tumours are generally well defined and surrounded by a thick fibrous capsule.

Microscopically, serous cystic neoplasms of the pancreas all share the same microscopic morphological features. Generally, the tumours are well defined with a rounded, lobulated pushing border, surrounded by compressed and atrophic pancreatic parenchyma. The cystic spaces are lined by a flat, single-cell layer of monomorphic epithelial, cuboidal neoplastic cells with minimal cytonuclear pleomorphism (Figure 5). Small intracystic papillary projections with minimal cellular crowding and overlapping are common. The cells exhibit a well-defined cytoplasmic membrane, and a moderate amount of clear to mildly eosinophilic, glycogen-rich cytoplasm. The nuclei are small, round to oval and centrally located, with dense chromatin and inconspicuous nucleoli.

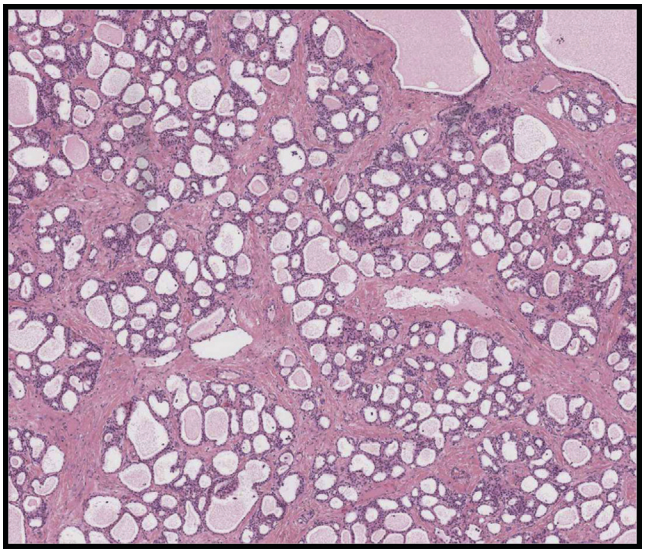

Figure 5 Serous cystic neoplasms have a honeycomb appearance and are lined by bland cuboidal epithelium often with clear cytoplasm.

Characteristically, there is no cytonuclear atypia, mitotic activity and necrosis. In SMAs, the intervening stroma ranges from delicate, highly vascularized strands to densely, broad fibrocollagenous tissue with hyalinization.

Molecular studies showed an important role of *VHL* tumour suppressor gene in pathogenesis of pancreatic SCNs. *VHL* gene allelic deletions (3p25 loss of heterozygosity) are identified in a large number of sporadic and von Hippel–Lindau-associated SCNs. Serous cystadenomas characteristically lack mutation in *k-ras* and *p53* genes.

Serous cystadenocarcinoma

Rare cases of pancreatic SCNs were reported as malignant. These tumours were associated with lymphovascular and perineural invasion, extension to the adjacent stomach and colon and, most importantly, metastatic disease to regional lymph nodes and liver. Mild nuclear atypia and more prominent papillary architecture are described in SCAs along with increased positivity for proliferation marker Ki-67 and overexpression of p53 protein. These features were believed to be a premalignant change and in keeping with the 3% estimated risk of malignancy in SCNs. However, because of the small number of documented cases, and rarity of the lesion, more work needs to be done to define the incidence and clinical behaviour of SCCs.

Management: unless the patient's general condition does not allow for surgical intervention, all pancreatic cystic neoplasms, including SCNs should be surgically removed. The reasons for this are that they grow progressively and increase in size, with subsequent risk of development of complications, such as obstruction of the biliary tree, or fistula and abscess formation. In addition, separating SCNs from pancreatic mucinous cystic neoplasms, which have a higher incidence of malignancy, cannot be done preoperatively in all cases.

Complete surgical resection is curative and the treatment of choice. There is no role for lymphadenectomy. Enucleation is another surgical option, and although it can be complicated by fistula formation, it has a comparable incidence of postoperative pancreatic fistula in patients treated by complete resection.

Mucinous cystic neoplasm

The most common cystic pancreatic neoplasm is the serous cystadenoma, followed by intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Other pancreatic neoplasms that may be cystic include: solid pseudopapillary tumour, ductal adenocarcinoma and neuroendocrine tumours.[19]

Clinical features: MCN comprise 9.7% of all neoplastic pancreatic cysts and have an age range of 20–95 years (mean 45–49 years). MCN occurs in women mainly, although some have reported occurrence in males. The female:male ratio is 10:1.

The most common presenting symptom is epigastric discomfort or pain. Many also present with an abdominal mass. Rare cases have been associated with Peutz–Jeghers and Zollinger–Ellison syndromes.

Pathology: MCN preferentially occurs in the tail of the pancreas, followed by body and head. In one series, 80% occurred in the tail, 13.8% in both the body and tail, 3.9% in the head and 2.3% in the body alone. MCN arising in the head are more likely to be malignant.

Size ranges from 1.5 to 30 cm while the mass ranges from 280 to 1100g (average 650 g). MCN are multilocular or unilocular with dilated blood vessels traversing the external surface. They are well circumscribed and have a fibrous capsule of variable thickness that may have foci of calcification. The cyst contents may vary in viscosity, colour and transparency. Papillary structures may be present. The cysts of MCN do not communicate with the pancreatic ductal system.

Microscopically, MCN are surrounded by a thick fibrous capsule, sometimes containing scattered atrophic ducts or acini (Figure 6). Frequently, there may be extensive denudation of the neoplastic epithelium requiring additional sampling of the specimen. In cystadenomas, a single layer of mucin secreting columnar cells with uniform basally orientated nuclei lines the cysts, often in a 'picket-fence' arrangement without significant cytological or architectural atypia very akin to its ovarian counterpart. Borderline lesions are lined by mucin-secreting cells showing moderate nuclear and architectural atypia: nuclear pleomorphism, prominent nucleoli, loss of nuclear polarity and complex papillary architecture. In-situ cystadenocarcinoma shows high-grade cytological atypia and cribriform architecture or cell bridges. Invasive cystadenocarcinoma consists of MCN with foci of unequivocal stroma invasion. Goblet cells, occasional Paneth cells and scattered endocrine cells may also be seen.

The epithelial lining is surrounded by a distinctive cellular stroma composed of spindle-shaped cells resembling the stroma seen in the ovary. Glands lined by mucinous-secreting epithelium may be present in the stroma but these should not be misinterpreted as invasion. The stroma frequently shows evidence of luteinization consisting of epithelioid cells with clear or eosinophilic cytoplasm.

It is now generally accepted that extensive sampling of MCN is essential to avoid missing areas of atypia or invasion. Some authors have recommended that the completely resected neoplasm should be entirely processed for histological examination.

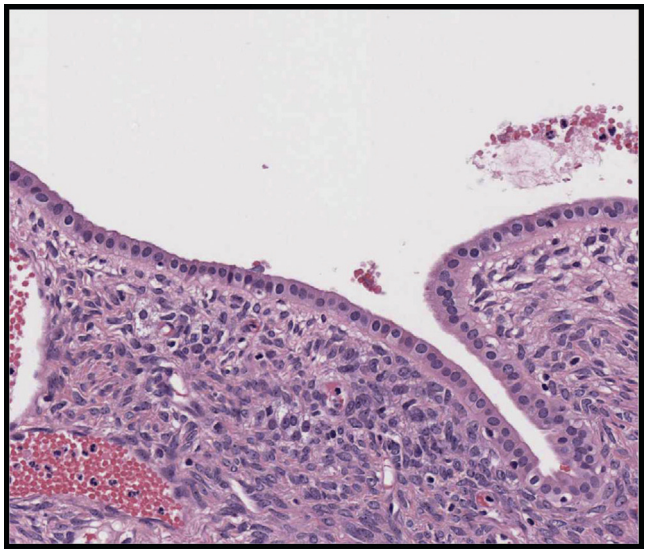

Figure 6 Mucinous cystic neoplasm is lined by columnar mucin producing cells and have a pathognomonic ovarian-type stroma.

Behaviour: histologically, benign MCN have been reported to metastasize or recur. However, in these cases, it has been suggested that careful and complete histological examination will often identify areas with atypical cytology and/or stromal invasion.

There appears to be a progression from cystadenoma to borderline MCN to in-situ cystadenocarcinoma to invasive cystadenocarcinoma. Therefore, if a non-invasive MCN is incompletely excised, the unresected component may progress to invasive cystadenocarcinoma.

Complete surgical excision has a 94% 5-year survival rate.

Osteoclastic giant cell tumour of the pancreas

Osteoclastic giant cell tumour (OGCT) of the pancreas is composed of undifferentiated epithelial or mesenchymal cells admixed with non-neoplastic osteoclast like giant cells. This lesion has a strong histologic resemblance to giant cell tumour of bone. OGCT has been described in association with ductal adenocarcinoma and mucinous cystadenocarcinoma of the pancreas.

This tumour tends to occur in the sixth and seventh decades of life with an equal gender distribution.

Grossly, these tumours are generally yellow-white with multiple areas of necrosis, haemorrhage and cyst formation. Most arise in the head of the pancreas and grow to a relatively large size, measuring on average from 5 to 8 cm.

Microscopically, the solid component consists of two cell types: monomorphic plump, epithelioid cells and multinucleated giant cells. The proportion of the cellular constituents vary with the mononuclear cells forming the vast majority of the tumour population (Figure 7). The mononuclear cells show mild to moderate pleomorphism, with intermediate sized nuclei. There is slight irregularity to nuclear contours with some cells having a reniform appearance while others contain longitudinal grooves. The cytoplasm of these cells varies from lightly eosinophilic to vacuolated. The multinucleate giant cells are interspersed and mingle imperceptibly with the mononuclear cells. These giant cells vary: some were small and contained 3 nuclei while others were much larger and contained up to 50 nuclei. These latter types conform to typical osteoclastic giant cells. The osteoclastic giant cells were characteristically concentrated in the inner aspects of the cystic areas and bordering on foci of haemorrhage. The mononuclear cells to be of epithelial derivation and to represent an undifferentiated carcinomatous component. The osteoclast like giant cells are thought to be 'reactive' and more of a secondary phenomenon.

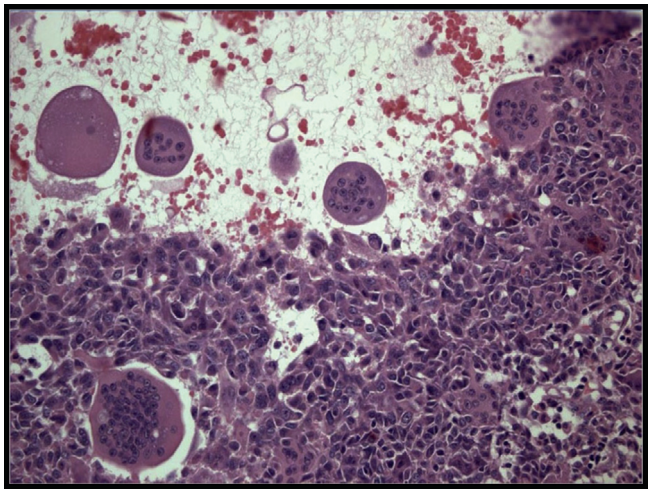

Figure 7 Osteoclastic giant cell tumour is characterized by large giant cells with numerous nuclei usually present around areas of haemorrhage and cyst formation.

Pancreatoblastoma

This is a primary malignant tumor of the pancreas that is composed of an epithelial component exhibiting acinar differentiation, nests or corpuscles or morules of squamoid cells and occasional endocrine cells.

Incidence: this is a very rare tumour and constitutes 0.1%–0.2% of all malignant tumours of the exocrine pancreas. However, it is the most common primary exocrine pancreatic neoplasm of childhood and makes up 25% of cases of paediatric pancreatic non-endocrine tumours. One third of cases are also noted in adults.

Clinical features: this tumour is usually encountered in children under the age of 10 years [mean: 4 years]. It occurs in both genders and is slightly more common in males. With regard to adults there is a wide age range and cases from 19 years to 78 years of age have been reported in the literature.

Rare associations of pancreatoblastoma include Beckwith–Wiedemann syndrome where the tumour is present at birth and is usually cystic. An adult case has been described with familial adenomatosis polyposis (FAP).

The presenting features are non-specific and related to the presence of an abdominal mass.

Pathology: pancreatoblastoma is usually a solitary mass that can occur anywhere in the pancreas and affects the head and tail equally. The tumour tends to be well-circumscribed, incompletely lobulated, soft and fleshy on cut section. Areas of calcification and cystic change may be present. The tumours range in size from 7 to 18 cm.

Microscopically, the tumour is surrounded by a partial fibrous pseudocapsule, but often invades into the adjacent pancreas, peripancreatic soft tissue or duodenum. It is made up of large lobules of highly cellular tissue separated by broad bands of fibrous tissue imparting a geographic pattern of lighter and darker staining cells.

The epithelial component is arranged in an acinar pattern sometimes with distinct lumina or a solid, sheet like pattern or squamoid corpuscles or morules.

The stroma tends to be very cellular in children and metaplastic osteoid and chondroid foci have also been described.

Behaviour: in one-third of cases, metastases are present at the time of diagnosis. These usually are found in the liver, lymph nodes, lung and peritoneum. The prognosis is better in children than adults especially for localized tumours that can be completely resected. However, if metastases are present, despite chemoradiation, the outcome is poor. In adults there is usually a rapid clinical course with a fatal outcome similar to that seen with acinar cell carcinoma.

Neuroendocrine tumours of the pancreas

Historically, the term carcinoid was introduced by Oberndorfer based on what he deemed to be 'little carcinomas' in the small

intestine. Other historical names used for this entity include: APUDoma, islet cell tumour/adenoma.

While the use of carcinoid is still in clinical practice, these tumours arise from cells of the dispersed endocrine system and their tumours are now designated as 'neuroendocrine tumours' (NETs) and this is the terminology that anyone dealing with these tumours should use. They all have malignant potential.[20,21]

Incidence: the incidence of NETs in the pancreas ranges from 0.4 to 1.0 per 100,000 people, while post-mortem studies have detected them in 0%–10% of post-mortems. In clinical and surgical series, NETs constitute about 5%–10% of all pancreatic neoplasms.

Clinical features: they are usually seen in patients over 30 years of age, with the preponderance of patients being between 40 and 60 years. There is no significant gender predilection. Clinically, they are divided into functioning and non-functioning PNETs depending on whether clinical symptoms due to hormone/peptide production are present or not. Symptomatology may be related to increased production of: gastrin (Zollinger–Ellison syndrome), insulin, vasoactive intestinal peptide (VIP), glucagon, somatostatin, growth hormone releasing hormone (GHRH), adrenocorticotrophic hormone (ACTH), 5-hydroxy tryptamine or serotonin (carcinoid syndrome), parathyroid hormone-related peptide (PTHrP) and calcitonin. It should be noted, however, that non-functioning tumours are commoner than the hormone-producing functional examples.

Hereditary forms or syndromes associated with pancreatic NET

An important part of the work up of patients with syndromic disease is to consider pancreatic pathology as part of the syndromic constellation of symptoms. There are several well-recognized syndromes associated with pancreatic NETs.

Multiple endocrine neoplasia (MEN) syndrome, type 1

This is an autosomal dominant condition and patients present with manifestations by 50 years of age. There are germline mutations of the *MEN-1* tumour suppressor gene located on chromosome 11q13 with resultant loss of a nuclear protein, menin, which suppresses cell proliferation normally. Pancreatic NETs occur in more than 60% of patients with MEN-1 and, intriguingly, manifest primary hyperparathyroidism before pancreatic lesions. MEN-1 tend to have multiple, small, non-functioning benign pancreatic NETs, often microadenomas. If a NET is functional, about 50% will be gastrin-producing and 20% insulin-producing. Parenthetically, MEN-1-associated NETs that produce gastrin are more common in the duodenum than the pancreas. MEN-1-associated pancreatic NETs tend to have a higher rate of postoperative recurrence and cause deaths in these patients.

von Hippel–Lindau disease

von Hippel–Lindau (VHL) disease is another autosomal dominant condition resulting from deletions or mutations in a tumour suppressor gene located on chromosome 3p25.5. VHL is characterized by retinal and central nervous system haemangioblastomas, cysts in the kidney, epididymis (papillary cystadenoma) and liver, haemangiomas of the adrenal, liver and lung, renal cell carcinoma, phaeochromocytoma and endolymphatic sac tumours. Pancreatic pathology in VHL is usually in the form of benign cysts and serous microcystic adenomas, which occur in 35%–70% of VHL patients. The frequency of pancreatic NETs, on the other hand, is less common and encountered in only about 10% of VHL patients.

VHL pancreatic NETs are multiple (usually up to five tumours present concurrently) and they are usually non-functional. However, we have observed a case of VHL in which these latter findings were present. VHL-associated PNETs characteristically are composed of clear cells or multi-vacuolated lipid-rich cells seen in varying proportions. Based on these histological findings, it is enough to investigate a patient for VHL if the clinical history is not apparent.

Neurofibromatosis type 1 (NF-1)

Very occasional cases of somatostatin-producing NETs have been encountered in the pancreas in NF-1 patients. These tumours are far commoner in the duodenum or periampullary region in patients with NF-1.

Tuberous sclerosis

Rare PNETs have been reported in patients with tuberous sclerosis.

Histogenesis/origin: the concept of a totipotential stem cell within ductules as a progenitor of both exocrine and endocrine cells is now well established and generally accepted. In addition, it is thought that both exocrine and endocrine pancreatic tissue can be derived from pre-existing, differentiated exocrine and endocrine cells.

Pathology: they can arise anywhere in the pancreas but the body and tail are the sites of preference. They form well-circumscribed masses that vary in size and it is important to remember, size does not predict behaviour. The smallest of pancreatic NETs have been noted to spread to lymph nodes and the liver.

The pathological evaluation of NETs entails light microscopic evaluation supplemented by immunohistochemistry (usually to assess whether a NET is functional and producing pancreatic hormones) and seeking specific molecular aberrations (these

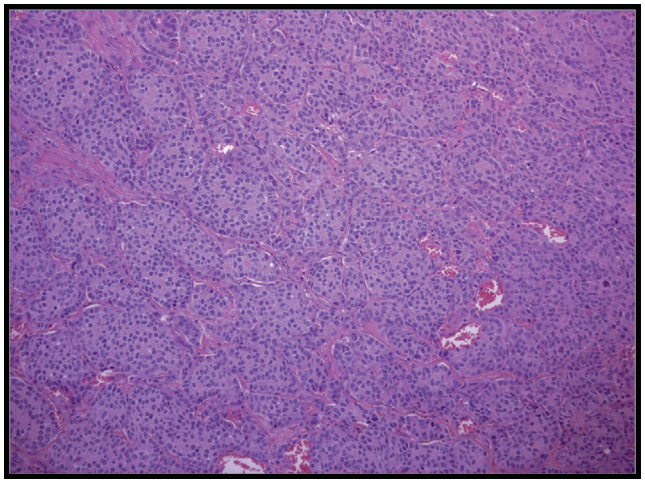

Figure 8 Neuroendocrine tumours are made up of uniform cells arranged in clusters or packets surrounded by a delicate vascularity which encircles the groups of neuroendocrine cells.

include genes such as *MEN-1*, *DAXX, ATRX*, *p53*, retinoblastoma (*Rb*) gene and *p16*) that impact on treatment and outcome.

There are three grades (grades 1–3) of well-differentiated pancreatic NET based on mitotic counts and Ki-67 proliferation indices. Finally, there is a separate high-grade (grade 3) neuroendocrine carcinoma.

Microscopy: the vast majority of PNETs conform to the typical neuroendocrine pattern with the well-recognized 'zellballen' or nested, packeted arrangement evident (Figure 8). Other patterns seen are trabecular, pseudoglandular or acinar and mixed patterns. The cells have typical cytological features: round to ovoid cells with eosinophilic, slightly granular cytoplasm and nuclei with a dispersed chromatin giving rise to the appellation: 'salt and pepper' chromatin pattern in nuclei. Insulin-producing pancreatic NETs are associated with amyloidosis.

Pancreatic neuroendocrine carcinomas are rare, high-grade aggressive cancers with a very poor prognosis and akin to their counterparts in the lung. ◆

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Practice points

- Pancreatic pathology is an important and sometimes under-recognized cause of patient morbidity
- Pseudocysts remain the commonest non-neoplastic cystic lesion of the pancreas
- Neoplastic cysts of the pancreas are readily identified with imaging techniques and pathological-radiological correlation is very helpful in obtaining an accurate diagnosis in biopsy material
- The pancreas is often the seat of metastatic disease such as melanoma, and this can sometimes be the initial presentation
- The role of neoadjuvant chemoradiation has transformed the landscape of pancreatic cancer assessment by pathologists. Regression is an important pathological parameter that needs to be assessed
- The latest grading of neuroendocrine tumours spans: well-differentiated, grades 1–3, based on mitotic counts and Ki-67 proliferation percentages. High-grade neuroendocrine carcinoma by definition is an aggressive cancer