Pancreatic pathology: an update

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) takes centre stage in the field of pancreatic pathology. It is the most common pancreatic neoplasm and carries a dismal prognosis with rising mortality rates. Tissue diagnosis focuses on the identification of PDAC and its distinction from non-neoplastic disorders such as chronic pancreatitis and rarer, less aggressive pancreatic neoplasms. Pathology also plays a key role in the assessment of well characterized macroscopic precursor lesions of PDAC: mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs). Endoscopic ultrasound-guided fine needle biopsies are becoming an increasingly valuable tool in the diagnosis of pancreatic lesions with paraffin-embedded material facilitating ancillary tests. Pathological examination of tissue samples from the pancreas allows typing and grading of neoplasms, and in resections will also provide information on stage, resection margin status and response to any neoadjuvant treatment given. It plays a vital role in the multidisciplinary care of patients with pancreatic diseases and, in the future, is very likely to form the basis for assessment of biomarkers in tissue sections for tumour genotype-specific treatment stratification. This review summarizes types of tissue samples, followed by descriptions of the most important non-neoplastic and neoplastic solid and cystic lesions including recent developments.

Keywords Cancer; neoplasia; pancreas; pancreatitis; pathology

Introduction

The pancreas is composed of acinar, ductal and endocrine cells with associated soft tissue resulting in a multitude of pathologies. Pancreatic ductal adenocarcinoma (PDAC), as the most common neoplasm of the pancreas, is of particular importance. PDAC is often regarded synonymous with pancreatic cancer. However, as approximately 85% of patients with pancreatic cancer present at an advanced stage where curative surgery is no longer possible, it is likely that most cases of 'pancreatic cancer' are in fact carcinoma in the head of pancreas that may also include a certain proportion of advanced carcinomas of intrapancreatic bile duct or the ampulla of Vater, which can resemble pancreatic ductal adenocarcinoma histologically. Pancreatic cancer is the 10th most common cancer in the UK with approximately 8000 new cases diagnosed every year. It has a very poor prognosis with a mortality essentially equalling incidence and a 5-year survival of less than 4% making it the lowest survival rate of the 21 most common cancers in the UK.[1]

The clinical presentation of pancreatic pathologies can be non-specific and abnormalities might only be detected on imaging. Radiologically detected localized abnormalities in the pancreas essentially fall either into a solid or a cystic category. PDAC is almost always a solid lesion and needs to be distinguished from chronic pancreatitis and other solid tumours. Eighty-five per cent of pancreatic cystic lesions are pseudocysts complicating pancreatitis. They need to be differentiated from cystic neoplasms some of which are precursors to pancreatic cancer. Histopathological examination plays a vital role in the diagnosis of non-neoplastic, pre-neoplastic and neoplastic conditions of the pancreas.

Pathological tissue specimens from the pancreas

Diagnostic samples

The retroperitoneal location of the pancreas, its close proximity to vital organs and the risk of pancreatitis pose a particular challenge for diagnostic tissue acquisition.

Endoscopic ultrasound (EUS) transgastric or transduodenal fine needle aspiration (FNA) has become the standard of care for solid pancreatic lesions with pooled sensitivities of 87% and specificities of 75–100%.[2] Material can be examined as direct spreads, liquid-based cytology preparations and/or cell block. Diagnostic yield will depend on endoscopist's experience, needle size/type and rapid on-site evaluation (ROSE), the latter being costly and often not practical. FNA diagnosis is challenging as it relies on cytological features such as cell type, nuclear and cytoplasmic appearances, cellularity and microarchitecture. It will be influenced by the expertise of the pathologist and requires close correlation with clinical and imaging findings. The main focus of EUS FNA is identification of PDAC which often exhibits discontinuous growth and dense desmoplastic stroma which may result in a low diagnostic yield. In well-differentiated PDAC the diagnosis becomes even harder, especially when relying purely on cellular changes without any intact tissue architecture. **EUS fine needle biopsies (FNBs)** contain small intact tissue fragments which can be processed as routine histology specimens. They have shown an equal sensitivity to FNA with slightly higher diagnostic yields and more paraffin embedded material for ancillary tests and research. There is a trend towards higher sensitivities and specificities in the diagnosis of PDAC and other lesions such as lymphomas, mesenchymal neoplasms, rare carcinomas and autoimmune pancreatitis, due to novel needle designs allowing acquisition of increasingly intact tissue cores (see Figures 1, 4 and 5).[3]

Common bile duct brush cytology obtained during ERCP can aid in the diagnosis of pancreatic tumours which have eroded the common bile duct but the sensitivity can be as low as 30%. **CT-guided, laparoscopic or open core biopsies** of the pancreas are taken if other diagnostic modalities have not been able to establish a diagnosis but carry an increased risk of peritoneal seeding.[2]

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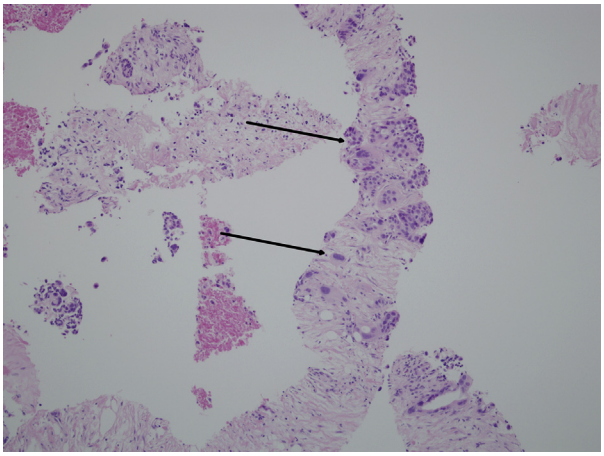

Figure 1 EUS-guided fine needle biopsy showing intact tissue core infiltrated by PDAC showing irregular glands and single large atypical cells in a desmoplastic stroma (arrows).

Intraoperative frozen sections of the pancreas are used to assess indeterminate primary lesions, tumour margins, presence of metastases and/or any unsuspected pathology. Frozen sections are available within minutes but the section quality is inferior to permanent paraffin embedded histology and distinction of reactive glands from adenocarcinoma may be very difficult. Good-sized, well-preserved specimens, pathologist's consistent application of diagnostic criteria and good communication between surgeon and pathologist will optimize results. Frozen sections of pancreatic neck margins have significant limitations. Further resection after positive neck margin frozen section for PDAC is not associated with improved overall survival.[4] Assessment of pancreatic duct involvement by intraductal papillary mucinous neoplasm (IPMN) may be hampered by epithelial denudation or suboptimal epithelial preservation. Skip lesions may also occur. The use of core biopsies for definite frozen section diagnosis should be best avoided as they may contain too little material.

Resection specimens

Pancreatoduodenectomy: either pylorus preserving or classical, is the most common resection specimen. The most frequent indication is periampullary carcinoma which includes PDAC of the head of pancreas, ampullary carcinomas, distal common bile duct carcinomas and occasional duodenal carcinomas. The role of pathology is to establish or confirm the diagnosis, inform prognosis, assess response to neoadjuvant treatment, facilitate selection of patients for adjuvant treatment including participation in clinical trials and allow correlation with radiological and surgical assessment. Pathology reports are also prerequisite for accurate data collection for cancer registries and epidemiological studies and allow audit and comparison of surgical practices. The cancer dataset for carcinoma of the pancreas, ampulla and distal common bile duct, published by the Royal College of Pathologists, provides guidelines for the consistent and accurate pathological examination of pancreatoduodenectomy specimens.[5] The most important prognostic factors to assess are tumour type, tumour size, differentiation, lymph node status and resection margins. Regarded as one of the most complex resection specimens in pathological practice, dissection of a pancreatoduodenectomy specimen requires confident identification and examination of key anatomic structures including any resected major vessels. Transection margins (duodenum/stomach, pancreatic neck and bile duct) need to be sampled and dissection margins (superior mesenteric vein, superior mesenteric artery and posterior retroperitoneal margin) differentially inked. Axial slicing is advocated, ideally with detailed photographic documentation, to allow visualization of the tumour in relation to key anatomic structures and comparison with cross sectional imaging. Macroscopic assessment and sampling is crucial for accurate microscopic evaluation and with regards to determining the origin of the tumour from pancreas, bile duct or ampulla by evaluating the location of the tumour epicentre. Problems ascertaining tumour origin may be encountered when the tumour is very extensive or poorly defined. Histological examination may provide additional clues such as periampullary or bile duct dysplasia but advanced PDACs, distal common bile duct and pancreato-biliary type ampullary carcinomas can look identical microscopically. In instances of uncertain tumour origin multidisciplinary approach is advocated. Due to its characteristically discontinuous growth, PDAC is usually more extensive microscopically than macroscopically, requiring extensive sampling of the dissection margins for accurate assessment of resection margin status. Total and subtotal pancreatectomies, distal pancreatectomies and local excisions as well as pancreatoduodenectomy for lesions other than periampullary carcinoma are less common but follow similar systematic dissection protocols.

Non-neoplastic solid lesions

Chronic pancreatitis

Chronic pancreatitis (CP) is a group of fibro-inflammatory processes of the pancreas which need to be distinguished from PDAC. CP occurs at a younger age of 30–40 and it is seen more commonly in men. Alcoholic chronic pancreatitis (ACP), accounting for approximately 80% of CP, is a chronic calcifying pancreatitis characterized by fibrosis, dilated ducts, calculi, fat necrosis and pseudocysts histologically. Ductular/tubular transformation of atrophic acini may present a challenge in the differentiation from PDAC. The overall preserved lobular pattern and lack of significant cytological atypia in atrophic tissue in the context of characteristic clinical history and imaging will allow safe distinction. Hereditary and tropical pancreatitis display similar histological features to ACP and an aetiological distinction could not be made based on histology. Obstructive chronic pancreatitis can be distinguished by lack of calculi. ACP and in particular hereditary pancreatitis carry an increased risk of pancreatic carcinoma, and obstructive chronic pancreatitis may be the result of an obstructing tumour. Therefore features of CP may co-exist with PDAC and if clinically there is a high index of suspicion of PDAC it has to be considered that a pathological diagnosis of CP in a biopsy could represent a sampling error.

In addition, there are two pathologically distinct types of chronic pancreatitis which clinically and on imaging can mimic PDAC: autoimmune pancreatitis (AIP) and paraduodenal pancreatitis.

Autoimmune pancreatitis: often presents with obstructive jaundice and a pancreatic mass clinically and distinction from PDAC is of utmost importance. AIP is characterized by a dramatic response to steroids and its accurate diagnosis will avoid unnecessary surgery. In contrast to other types of CP it is characterized by duct

