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CORRESPONDENCE

Intraductal tubulopapillary neoplasm of pancreas with associated invasive carcinoma, lymph node, rectal and hepatic metastases

Sir,

Intraductal tubulopapillary neoplasm (ITPN) is a rare pre-malignant pancreatic tumour comprising 0.9% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms in the largest series published.[1] Recognised as a specific diagnostic entity for over a decade by Japanese investigators,[2] this tumour was not well recognised by Western pathologists until recently and only incorporated into the WHO classification of tumours of the digestive system in 2010 as an intraductal neoplasm distinct from other intraductal tumours, in particular, intraductal papillary mucinous neoplasms (IPMN).[3] An invasive component, designated 'ITPN with an associated invasive carcinoma' in the 2010 WHO Classification was found in a small minority of reported cases and the malignant potential and behaviour of this tumour is not well characterised. We describe the histological, immunohistochemical and cytological features of an intraductal tubulopapillary neoplasm of pancreas with associated invasive carcinoma, and subsequent rectal and liver metastases in a 55-year-old man.

The patient was previously well and presented with left sided upper abdominal pain. Endoscopic ultrasound and subsequent abdominal computed tomography (CT) scan showed a cystic lesion in the pancreatic tail. A distal pancreatectomy, splenectomy and partial gastrectomy was performed.

Gross examination of the surgical specimen showed a friable, poorly fixed, white-grey tumour, 100 mm in maximum dimension, centred within the pancreas with infiltration through the wall of the adjacent stomach and into splenic parenchyma (Fig. 1A). Microscopic examination (Fig. 1B–F) showed areas typical for ITPN plus extensive associated invasive carcinoma. The intraductal component consisted of well formed, closely packed tubules and cribriform structures (Fig. 1B). Neither intra-cellular nor extra-cellular mucin was present on haematoxylin and eosin (H&E) and periodic acid-Schiff (PAS)-diastase staining. Occasional tubulopapilliform structures were identified. The tumour cells were cuboidal to columnar with rounded nuclear contours, pale chromatin and small nucleoli (Fig. 1C,D). The cytoplasm varied from palely eosinophilic to amphophilic. Patchy necrosis was present in the intraductal component and as a focal finding in the invasive component of the tumour, including within metastatic tumour in local lymph nodes. The invasive portion strongly resembled the intraductal component with a crowded tubular and cribriform architecture and infiltrated widely throughout the pancreatic tissue, into gastric muscularis propria and splenic parenchyma. Infrequent mitotic figures were present in both the intraductal and invasive components [averaging 1/10 high power fields (HPF)]. Two peripancreatic lymph nodes contained metastatic tumour deposits with a tubular and cribriform appearance. On immunohistochemical examination the neoplastic cells displayed positivity for CK7, CK19 and MUC1, while MUC5AC, MUC2, synaptophysin, chromogranin, CA19-9, CD56, CD10, nuclear β-catenin and BRAF V600E were negative.

Approximately 2 years after pancreatic resection the patient complained of tenesmus. CT scanning demonstrated a 6 cm mass in the rectovesicle pouch with uptake on a positron emission tomography (PET) scan. At laparoscopy no mass was evident, colonoscopy demonstrated an extrinsic mass indenting the anterior rectal wall, and core biopsies were performed. The lesion appeared isolated and resectable and he underwent neoadjuvant chemoradiation. Subsequent abdominal CT scan demonstrated multiple low density hepatic lesions consistent with metastases. Core and fine needle aspiration biopsies of one of the liver lesions were performed.

Core biopsies from the rectal mass showed a few clusters of hyperchromatic cells with cribriform architecture, strong immunostaining for CK7, negative immunostaining for CA19-9 and no mucin. Liver core biopsy showed tumour deposits consisting of variably sized tubular and cribriform structures with a small amount of fibrotic stroma (Fig. 1F). Many tubules contained neutrophils and foci of necrosis. The neoplastic cells were cuboidal to low columnar with high nucleocytoplasmic ratios, nuclear crowding and small nucleoli, closely resembling those seen in the previously resected pancreatic tumour. FNA smears of the hepatic tumour were highly cellular and contained medium-sized cells arranged in sheets, branching tubular structures and some papilliform groups (Fig. 1E). Nuclei were moderately pleomorphic, round to oval with occasional indentations, a fine chromatin pattern and small nucleoli. No mucin vacuoles were seen and the cytoplasm was pale and poorly defined.

Given the confirmed irresectable metastatic disease, the rectal lesion was not removed. He was commenced on combination chemotherapy and remains working and relatively asymptomatic almost 3 years after original diagnosis.

The primary tumour showed morphological features diagnostic of ITPN with the typical immunohistochemical profile of that entity. The tumour lacked intraluminal and cytoplasmic mucin, the architecture was tubular and tubulopapillary rather than papillary, and there was positive immunostaining for MUC1 while MUC2 and MUC5AC were negative, features which distinguish ITPN from IPMN.[1,3] The differential diagnosis of acinar cell carcinoma was excluded by the absence of PAS-diastase positive cytoplasmic granules combined with strong diffuse CK7 and CK19 immunostaining, while the lack of staining with neuroendocrine markers ruled out a neuroendocrine tumour. Solid pseudopapillary neoplasm was excluded based on the absence of typical morphological features of that entity, such as nuclear grooves, cytoplasmic PAS-diastase positive inclusions and aggregates of foamy macrophages, as well as negative immunostaining with CD10, CD56 and for nuclear β-catenin.

ITPN occurs over a wide age range in adults with approximately equal sex distribution and is most commonly found in the pancreatic head; however, tumours are also reported in the pancreatic body and tail, and rarely involve the entire duct system.[1,4,5] As in our case, the typical macroscopic findings are of solid, nodular masses within the dilated main pancreatic duct with or without involvement of branch ducts, the accessory pancreatic duct or common bile duct and an absence of intraductal mucin.[1,2,4,6]

The histological features of ITPN are well illustrated by this case. Key features include the presence of tumour nodules

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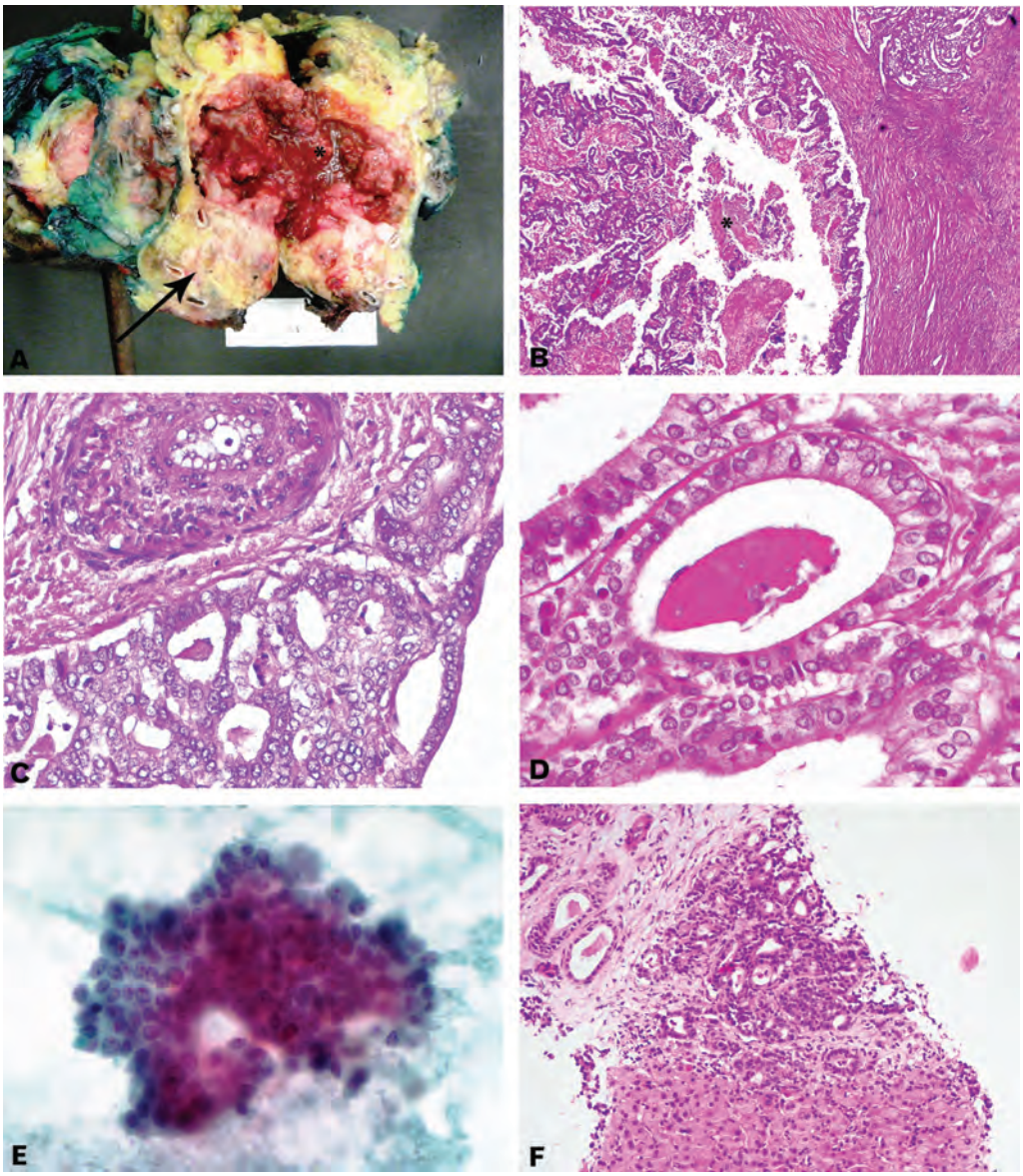

Fig. 1 (A) Macroscopic appearance of the pancreatic tail lesion. The tumour consists of a poorly fixed large intraductal portion (*) and adjacent solid invasive nodules of tumour (arrow). (B) The intraductal portion of the tumour (*) shows tubulopapillary architecture with rounded contours and the adjacent invasive portion consists of irregularly shaped nodules of crowded tubular structures (H&E). (C) The invasive component adjacent to a thick walled pancreatic artery retains a tubular and cribriform appearance (H&E). (D) High power view of typical intraductal tubular and cribriform arrangements composed of cuboidal and low columnar tumour cells with eosinophilic cytoplasm, raised nucleocytoplasmic ratios and mild-moderate nuclear pleomorphism (H&E). (E) Smear preparations from aspiration of a liver lesion contain crowded papilliform tissue fragments with focal tubule formation. Cells show moderate nuclear variability with round to oval nuclei, fine chromatin and small nucleoli. Cytoplasm is pale and poorly defined and no mucin vacuoles were identified (Papanicolaou stain). (F) Metastatic disease within liver showing retention of tubular and cribriform architecture (H&E).

within expanded ducts showing crowded tubular and cribriform structures, absence of cytoplasmic or extra-cellular mucin, foci of necrosis and cuboidal tumour cells with small nucleoli.[1,3,7] Cystic areas are uncommon, but when present may contain tubulopapillary or papillary projections. Mitotic activity is variable but often higher than in this case with counts up to 9 per 10 HPF reported; high mitotic score and Ki-67 proliferative index are associated with invasion.[1] Characteristically ITPNs have uniformly high grade dysplasia/atypia without adjacent or intermixed lower grade areas.[1,8] Tumours with a component of invasive carcinoma are described in a minority of published cases and retain a tubulopapillary appearance[1] which in this case is preserved between the primary invasive carcinoma and lymph node, rectal and liver metastases. Preservation of tubulopapillary and cribriform architecture and the limited desmoplasia create difficulty in recognising invasion. Involvement of adjacent structures, such as duodenum, or stomach as in our case, is helpful if present and the presence of venous invasion is diagnostic of invasion.[1,2] Foci of tumour adjacent to a pancreatic blood vessel implies extraductal spread since the pancreatic ducts do not normally accompany muscular vessels.[9]

Immunohistochemical profiling may be used as an adjunct to diagnosis and is summarised in a recent review paper.[7] ITPNs show strong positive immunoreactivity with either cytokeratin 7 and/or 19, plus membrane positivity with MUC1 and sometimes MUC6.[1] Immunopositivity for CA19-9 is present in approximately half of cases whereas CEA is negative.[5] Analysis of the underlying molecular aberrations of intraductal pancreatic tumours is another potential diagnostic aid: ITPNs frequently show strong expression of phosphorylated AKT by