

Lipid-rich variant of pancreatic endocrine tumour with inhibin positivity and microscopic foci of microcystic adenoma-like areas: emphasis on histopathology

Anuradha Calicut Kini Rao¹, MD, DNB, Vidya Monappa¹, MD, DNB, Prashanth Shetty², MS

ABSTRACT Pancreatic endocrine tumours (PETs) are uncommon tumours with typical morphology characterised by relatively uniform cuboidal cells arranged in nests and festoons, with distinctive nuclear salt-and-pepper chromatin. A lipid-rich variant poses diagnostic difficulties in the midst of other pancreatic tumours and metastatic goblet cell carcinoid. A 22-year-old man presented with symptoms of abdominal pain and jaundice. His liver function test and blood glucose level were normal, but computed tomography of the abdomen suggested the presence of a tumour in the head of the pancreas. Specimen obtained by pancreaticoduodenectomy revealed an infiltrating yellow-tan tumour composed of nests and a cribriform arrangement of polygonal vacuolated cells with pyknotic nuclei, along with focal classical areas of PET. Two foci of early serous microcystic adenoma were seen. Immunohistochemistry contributed to the arrival of a conclusive diagnosis. Von Hippel-Lindau disease was excluded in our patient, as other supportive classical features of the syndrome were absent.

Keywords: lipid-rich variant, microcystic adenoma, pancreatic endocrine tumour, von Hippel-Lindau
Singapore Med J 2013; 54(2): e31–e34

INTRODUCTION

Pancreatic endocrine tumours (PETs), traditionally designated as islet cell tumours, account for less than 3% of all pancreatic tumours. Patients may present clinically with symptoms related to its often functional nature, or jaundice secondary to obstruction. Histologically, PETs have an organoid growth pattern similar to other endocrine tumours in the gastrointestinal tract, characterised by uniform cells arranged in trabecular, ribbon-like, acinar, alveolar or gyriform patterns with distinctive salt-and-pepper chromatin. The lipid-rich variant of PET is an uncommon variant that has cells with abundant clear, vacuolated cytoplasm. Although reports exist in the literature, association of the lipid-rich variant of PET with von Hippel-Lindau (VHL) disease remains controversial.

CASE REPORT

A 22-year-old Indian man presented with complaints of pain in the abdomen and intermittent vomiting subsisting over a duration of two months. The patient had a history of jaundice two months prior to presentation. The results of the laboratory investigations were as follows: fluid amylase 767 U/L; total bilirubin 4.3 mg/dL; and aspartate transaminase and alanine transaminase at mildly elevated levels of 220 mEq/L and 168 mEq/L, respectively. On abdominal examination, a hard mass measuring 5 cm × 5 cm was palpated in the right subcostal and epigastric region. Upper gastrointestinal endoscopy showed evidence of extrinsic compression at the pylorus. Computed tomography (CT) revealed a lobulated, intensely enhancing mass

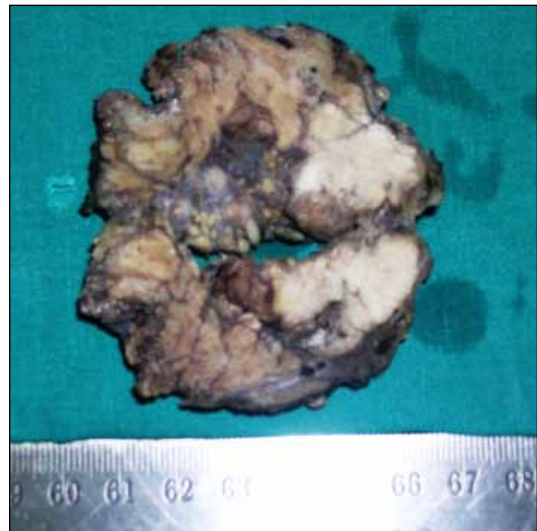


Fig. 1 Photograph of the cut section of the specimen shows an infiltrating tumour with yellow-tan areas, found in the head of the pancreas.

in the region of the head and uncinate process of the pancreas with punctate calcifications. Other viscera were normal. The possibility of a neuroendocrine tumour (nonfunctioning type) was suggested.

Specimen obtained by Whipple's pancreaticoduodenectomy was sent for histopathological examination. The cut section of the patient's pancreas revealed the presence of an infiltrating tumour measuring 3.0 cm × 2.5 cm with yellow-tan areas (Fig. 1). Microscopically, the tumour showed extensive areas of swollen, vacuolated clear cells with microvesicles indenting the often eccentric nucleus (Fig. 2), which were oil red O stain positive

¹Department of Pathology, ²Department of Surgery, Kasturba Medical College, Manipal University, Manipal, India.

Correspondence: Dr Anuradha CK Rao, Professor, Department of Pathology, Kasturba Medical College, Manipal University, Manipal, Karnataka 576104, India. anuchenna@yahoo.com

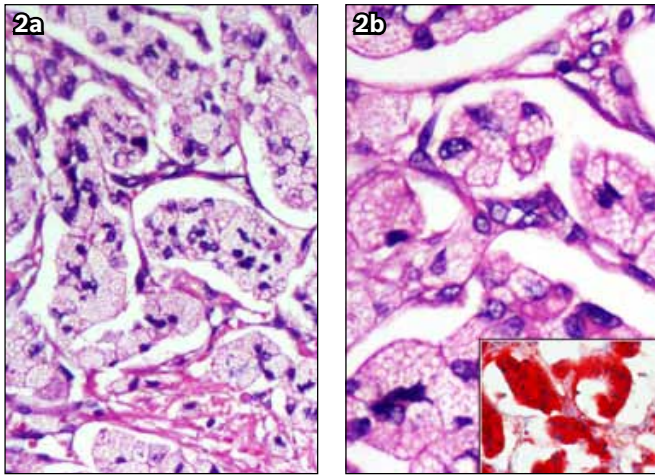


Fig. 2 Photomicrographs show (a) the tumour cells composed of swollen vacuolated clear cells, with microvesicles indenting the often eccentric nucleus (Haematoxylin & eosin, $\times 200$); and (b) swollen cells with microvesicular cytoplasm (Haematoxylin & eosin, $\times 400$). The inset in (b) shows oil red O positivity in the cell cytoplasm.

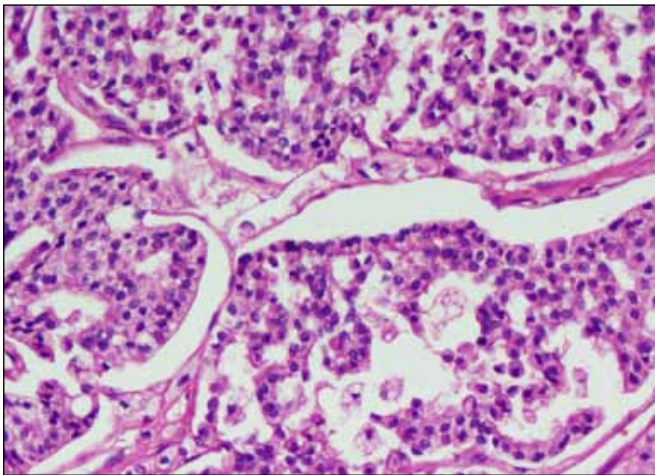


Fig. 3 Photomicrograph shows the tumour with typical PET morphology (Haematoxylin & eosin, $\times 200$).

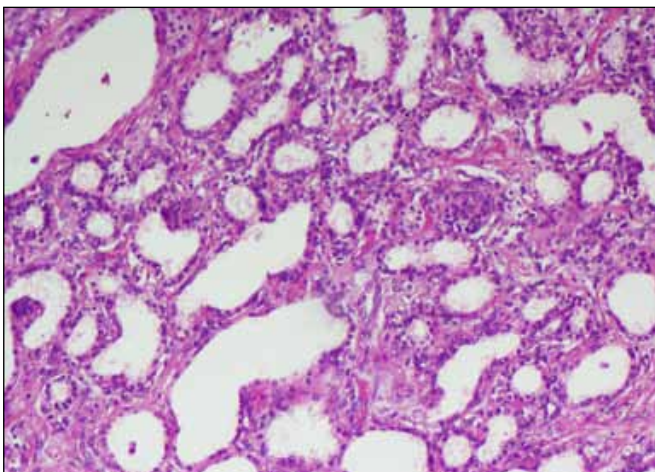


Fig. 4 Photomicrograph shows the foci of the microcystic adenoma-like areas (Haematoxylin & eosin, $\times 100$).

(Fig. 2b, inset) and periodic acid-Schiff-negative. An occasional bizarre cell, interspersed cells with signet ring morphology and rare mitosis ($< 1/10$ hpf) were seen. Elsewhere, typical PET with insular inlands, nests, trabeculae, gyriform patterns and

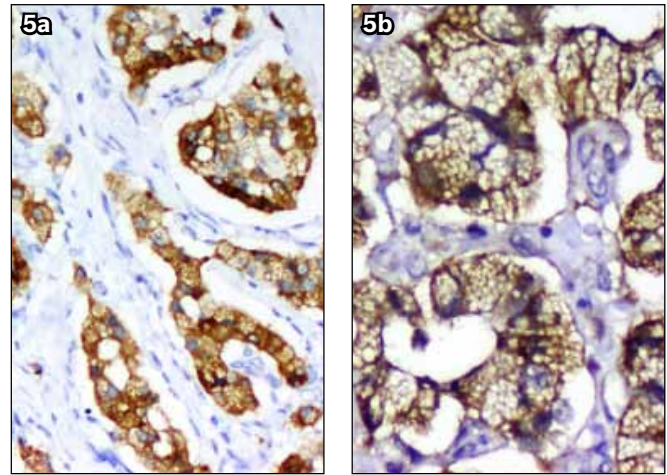


Fig. 5 Photomicrographs of the tumour cells show (a) diffuse positivity for chromogranin (Chromogranin, $\times 200$); and (b) moderate positivity for inhibin (Inhibin, $\times 400$).

focal cribriform islands of low columnar to polygonal cells, with moderate to abundant eosinophilic granular cytoplasm, small nucleus, stippled chromatin and inconspicuous nucleoli, was noticed. The interstitium showed delicate fibrous septae enveloping tumour nests, along with thick interspersed fibrous bands with hyalinisation (Fig. 3). Two foci (the larger of which measured $0.2 \text{ cm} \times 0.1 \text{ cm}$) also showed the presence of closely packed cystic spaces and macroglands lined by cuboidal cells, with vacuolated cytoplasm suggestive of microcystic adenoma-like areas (Fig. 4). Immunohistochemistry (IHC) showed tumour cells exhibiting strong and diffuse positivity for chromogranin (CH) and synaptophysin (SY), moderate positivity for inhibin (INH), focal positivity for cytokeratin (CK)-7, and an MIB score of 7/100 cells (Fig. 5). The microcystic adenoma-like areas were positive for CK, but negative for SY and INH.

A final diagnosis of lipid-rich variant of PET – well-differentiated neuroendocrine carcinoma – was made based on our histological and immunohistochemical findings. The patient recovered well, and was symptom-free at his last follow-up.

DISCUSSION

PETs are rare tumours with variable and complex morphology, and can be clinically functional or nonfunctional. Functional endocrine tumours are easier to distinguish from other nonendocrine pancreatic primary and metastatic tumours. Nonfunctioning tumours, however, pose a dilemma to the pathologist, who has to consider the complex variants of PETs and the plethora of PET mimics. Functional tumours are usually small, as they present early with syndromic manifestations related to the secreted hormone (e.g. insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma and pancreatic polypeptidoma). Nonfunctional tumours usually present late with symptoms related to mass effect.⁽¹⁾

A wide variety of imaging methods have been described in the literature for the localisation of PETs and detection of metastases, including CT, magnetic resonance imaging,

intraoperative ultrasonography, endoscopic ultrasonography and angiography. CT is the most widespread diagnostic tool, with a high sensitivity of 78% for the detection of lesions. PETs are typically isointense with increased vasculature.⁽¹⁾ The radiologic findings of lipid-rich variant of PET have not been described in the literature. Thus, differentiating between the variants rests on microscopy.

PETs can be a component of four well-established syndromes: multiple endocrine neoplasia type 1, VHL, neurofibromatosis type 1 and tuberous sclerosis complex. PET alone in the absence of other lesions rules out the possibility of a syndromic association. However, IHC positivity of INH requires a search for other features of VHL syndrome due to their documented association.⁽²⁾ VHL disease is a rare autosomal dominant disorder characterised by the development of cystic lesions and endocrine tumours in the pancreas, haemangioblastoma in the central nervous system and retina, renal cell carcinoma, pheochromocytoma, renal cysts and epididymal cystadenoma.^(3,4) VHL-associated pancreatic cystic lesions are thought to be multifocal microcystic adenoma and simple cyst, while pancreatic lesions are thought to be an early manifestation of VHL. Although microcystic adenoma and PETs do coexist in VHL, there have been reported cases where a similar association was recorded in the absence of VHL mutation. Serous cystadenomas in such cases could be oligo- or multicystic and show cystic spaces lined by cuboidal cells with clear cytoplasm, with vesicular nuclei located predominantly in the head, few in the body and occasionally as a diffuse process.⁽⁵⁾ PET could be a nodule within or separate from it. In our case, however, the predominant tumour was a PET with microscopic foci of microcystic adenoma-like areas. Such nascent or early areas seen within a lipid-rich PET have not yet been reported in the literature, making this the first such reported case.

PETs in VHL are nonfunctional, but have malignant potential and are morphologically of clear cell type.⁽⁶⁾ However, the results of an exhaustive study by Singh et al⁽⁷⁾ on lipid-rich variant of PETs was INH negative and not found to be associated with VHL. In light of this, our present case assumes significance, as the lesion detected was an INH-positive lipid-rich variant of PET, with focal areas suggestive of early microcystic adenoma (multifocal), but without any other features that suggest VHL association. PETs can exhibit a variety of morphological appearances, which often require careful differential diagnostic consideration. A variety of histological variants of PET have been reported – spindle cell, oncocytic, rhabdoid, pleomorphic, pigmented, lipid-rich and clear cell – with the latter found particularly in patients with VHL syndrome.⁽⁸⁾ The main significance of these morphological variants lies in the awareness of their existence and distinction from other tumour entities. Most are, however, considered of no prognostic relevance.

Lipid-rich variant of PET was first described by Ordonez and Silva in 1997⁽⁹⁾ as a distinct subtype of PET. Singh et al⁽⁷⁾ had, in their landmark study of this category, differentiated this lesion

from the VHL-associated clear cell variant of PET. The foamy lipid-rich microvesicular cytoplasm is extremely uncommon for endocrine neoplasia located outside of the adrenal gland and thyroid, thus contributing to its diagnostic difficulty, especially in small biopsies. The pathogenesis of lipid vesicles is thought to be a degenerative change. Morphologically, the lipid-rich variant differs from the usual PET in many respects: (a) lack of salt-and-pepper chromatin pattern in round to pyknotic nuclei; (b) diffuse growth pattern; and (c) vasculature with a more sinusoidal quality. The present case showed focal typical PET, facilitating the final diagnosis. Ordonez and Silva⁽⁹⁾ further described intracytoplasmic periodic acid-Schiff positive eosinophilic globoid inclusions with strong staining on IHC for $\alpha 1$ -antitrypsin. This feature was suggested as a marker in cases of metastasis, especially to the liver. Ultrastructurally, these tumour cells show lipid droplets, dilated cisterns of endoplasmic reticulum and dense core neurosecretory granules.^(7,9)

In the present case, the various differential diagnoses considered were: (a) goblet cell carcinoid (GCC); (b) acinar cell carcinoma (ACC); (c) foamy gland pattern of pancreatic ductal carcinoma; (d) clear cell variant of papillary and solid epithelial neoplasm (PSEN); and (e) clear cell PET. The absence of cytoplasmic mucin on histochemistry ruled out GCC. Immunohistochemical positivity for pan-endocrine markers (CH and SY) helped to rule out pancreatic ductal carcinoma and ACC. Immunohistochemically, ACC shows positivity for CK-18, trypsin and amylase.⁽¹⁰⁾ The lack of any cystic or pseudopapillary histomorphological features helped to exclude PSEN. The presence of clear cytoplasm can contribute to the misdiagnosis of clear cell variant of PET. However, on closer observation, the cells showed microvesicular cytoplasm with positivity for fat stains. The various immunohistochemical markers useful for the diagnosis of PETs include SY, CH and CD56. The Ki-67 index is recommended to gain knowledge on the proliferative activity of the tumour. Hormonal markers such as insulin and glucagon can be examined in functional tumours. In the present case, the tumour was nonfunctional and a thorough clinicoradiological investigation did not reveal any other tumour. CK-19 has been proposed as a marker for the aggressiveness of PETs.

The World Health Organization's classification of PET⁽¹¹⁾ categorises these tumours into four groups: (a) well-differentiated, benign neuroendocrine tumour – confined to the pancreas, < 20 mm, < 2 mitosis/10 hpf; (b) well-differentiated neuroendocrine tumour, with uncertain malignant potential – confined to the pancreas with ≥ 1 of the following features: 20 mm, 2–10 mitosis/10 hpf, vascular/perineural invasion; (c) well-differentiated, low-grade, malignant neuroendocrine carcinoma – gross local invasion and/or metastasis; and (d) poorly differentiated neuroendocrine carcinoma – > 10 mitosis/10 hpf. This categorisation has been found to be of prognostic significance. Our case fell into the third category. In the absence of other visceral lesions characteristic of VHL syndrome, VHL was excluded in our patient.

In conclusion, a lipid-rich tumour is a rare and distinct histological variant of PET, which shows abundant microvesicular vacuolated lipid-rich cytoplasm. The absence of characteristic salt-and-pepper chromatin and diffuse proliferation of the cells may cause diagnostic confusion with other tumours. Mistaking it for the clear cell variant of PET is possible and differentiating them is of significance, due to the common association of clear cell variant with VHL disease. The demonstration of cytoplasmic lipid and positivity for pan-endocrine markers plays an important role in arriving at the right diagnosis. Features such as INH positivity and associated microscopic foci suggesting an early lesion or nascent form of microcystic adenoma occurring in concert are unusual phenomenon hitherto unreported in association with this variant.

REFERENCES

1. Reznick RH. CT/MRI of neuroendocrine tumours. *Cancer Imaging* 2006; 6:S163-77.
2. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: Advances in molecular pathogenesis, diagnosis, management and controversies. *Cancer* 2008; 113(7 Suppl):1807-43.
3. Tamura K, Nishimori I, Ito T, et al. Diagnosis and management of pancreatic endocrine tumor in von Hippel-Lindau disease. *World J Gastroenterol* 2010; 16:4515-18.
4. Neumann HP, Dinkel E, Brambs H, et al. Pancreatic lesions in Von-Hippel-Lindau syndrome. *Gastroenterology* 1991; 101:465-71.
5. Blandamura S, Parenti A, Famengo B, et al. Three cases of pancreatic serous cystadenoma and endocrine tumour. *J Clin Pathol* 2007; 60:278-82.
6. Musso C, Paraf F, Petit B, Archambeaud-Mouvieroux F, Valleix D, Labrousse F. [Pancreatic neuroendocrine tumors and Von Hippel Lindau disease]. *Ann Pathol* 2000; 20:130-3. French.
7. Singh R, Basturk O, Klimstra DS, et al. Lipid-rich variant of pancreatic endocrine neoplasms. *Am J Surg Pathol* 2006; 30:194-200.
8. Verbeke CS. Endocrine tumours of the pancreas. *Histopathology* 2010; 56:669-82.
9. Ordonez NG, Silva EG. Islet cell tumour with vacuolated lipid-rich cytoplasm: a new histological variant of islet cell tumour. *Histopathology* 1997; 31:157-60.
10. Loos M, Bergmann F, Bauer A, et al. Solid type clear cell carcinoma of the pancreas: differential diagnosis of an unusual case and review of the literature. *Virchows Arch* 2007; 450:719-26.
11. Delellis RA, Lloyd RV, Heitz PU, Eng C, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Tumour of Endocrine Organs. Lyon: IARC Press, 2004: 175-207.