CASE REPORT

Oncocytic Neuroendocrine Tumour of the Pancreas and Duodenum: Two Case Reports with Review of the Literature

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ABSTRACT

Neuroendocrine tumours are a heterogeneous group of tumours originating in various anatomical locations. The management of this disease represents a significant challenge because of the heterogeneous clinical presentations and varying tumour biology. Oncocytic variant of neuroendocrine tumour is rare and the diagnosis is based on histopathological analysis following surgery. The lack of specific clinical features makes preoperative diagnosis difficult. We report two cases of oncocytic variant of neuroendocrine tumours and review of the literature of this subtype of neuroendocrine tumour.

INTRODUCTION

Neuroendocrine tumours (NET) s are a heterogeneous group of neoplasms originating in various anatomical locations. Pancreatic neuroendocrine tumours (PNETs) account for 2-3% of all pancreatic neoplasms [1, 2]. Duodenal NETs comprises of up to 3% of all duodenal tumours and 2% - 3% of all endocrine tumours [3]. The management of this disease represents a significant challenge because of the heterogeneous clinical presentations and varying tumour biology [1]. Although NETs are usually sporadic, they can be associated with genetic syndromes such as multiple endocrine neoplasia type 1, neurofibromatosis type 1 and Von Hippel-Lindau syndrome. The overall survival for patients with NETs is much better compared to patients with adenocarcinomas [4]. Oncocytic variant of NET is rare and the diagnosis is based on histopathological analysis following surgery. The lack of specific clinical features makes preoperative diagnosis difficult.

We report two cases of oncocytic variant of NET with review of the literature of this subtype of NET.

CASE REPORTS

Case #1

A fourty-one-year-old Caucasian woman presented with a 4 week history of epigastric pain. Clinical examination and laboratory analysis were unremarkable. Ultrasound scan showed an indeterminate abdominal mass. Contrast enhanced computed tomography (CT) identified an enhancing mass involving the proximal body in the pancreas measuring 6.2 cm x 4.8 cm (**Figure 1**). Endoscopic ultrasound (EUS) and fine needle aspiration (FNA) showed a well differentiated NET. The tumour cells showed positive immunopositivity for CD56 and chromogranin A. Proliferative index by Ki67 was <2%. Metaiodobenzylguanidin (MIBG) and Octreotide scan revealed increased activity within the mass in the pancreas. Following discussion at the multidisciplinary team meeting, the patient underwent an extended distal pancreatectomy and splenectomy.

Pathological examination (**Figure 2**) showed a macroscopically well circumscribed, encapsulated tumour

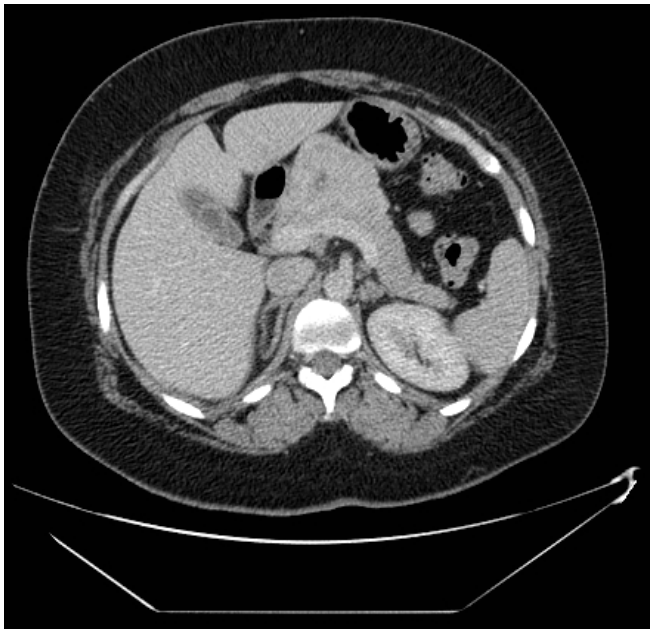

Figure 1. Pre-operative CT of the abdomen demonstrating the mass arising from the proximal body of the

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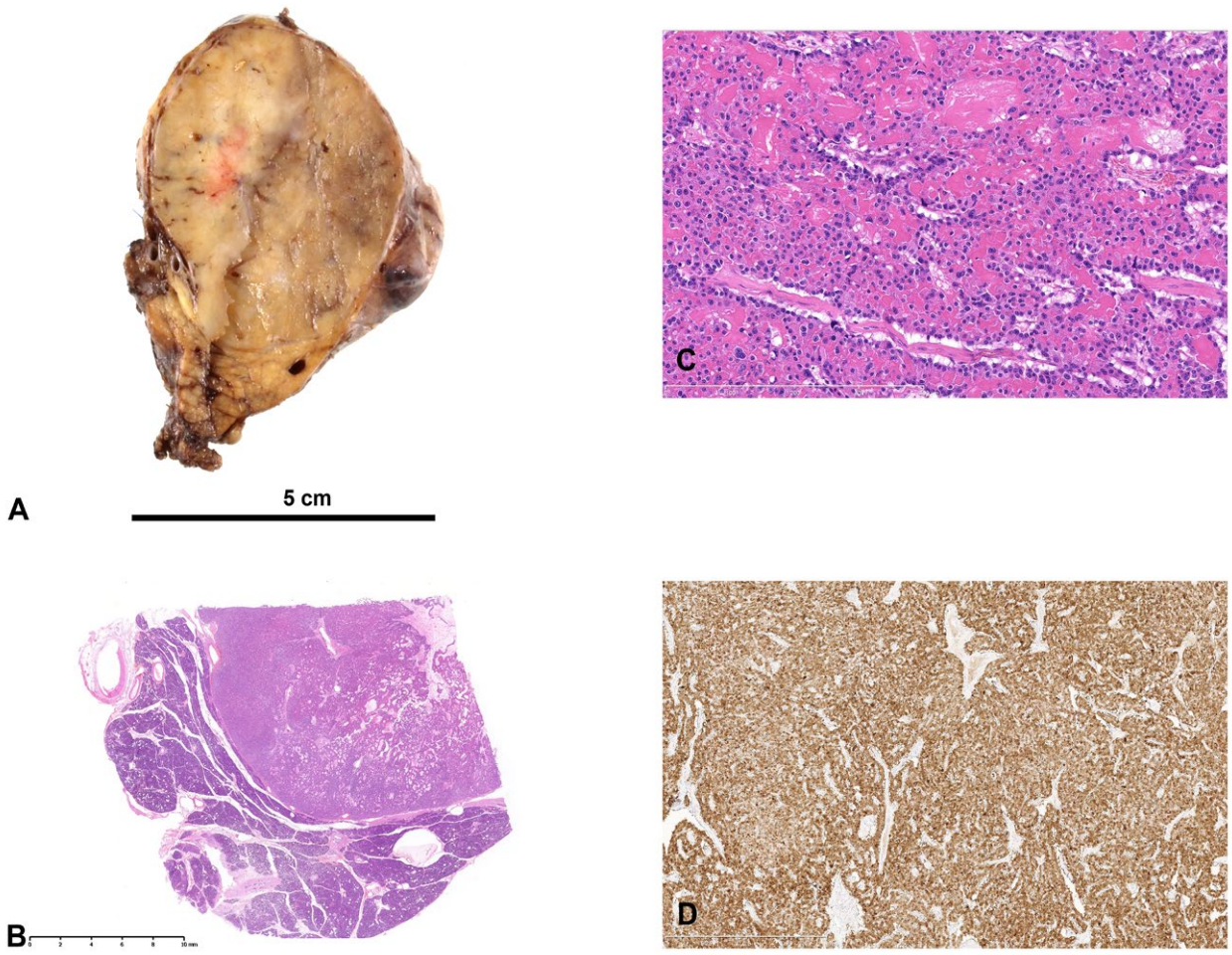

Figure 2. a. Section through solid pancreatic tumour, **b.** Well circumscribed tumour (Haematoxylin & eosin [H&E], original magnification), **c.** Oncocytic tumour cells in a trabecular pattern (H&E, x5), **d.** Positive immunostaining for chromogranin A (x5).

measuring 60mm in maximum dimension. Microscopic examination revealed the tumour to be composed of large cells with granular, eosinophilic cytoplasm and enlarged nuclei containing coarse, stippled chromatin with occasional prominent nucleoli. These cells showed a predominantly trabecular architecture with both nested and gyriform patterns seen focally. Mitotic activity was inconspicuous with a formal mitotic count of 0 mitoses in 10 high power fields. There was no evidence of vascular or perineural invasion. Nine lymph nodes were examined, none of which were involved by tumour.

Immunohistochemical staining showed tumour cell positivity for PGP 9.5, chromogranin A, CD56, CK19, Cam 5.2, E-cadherin and alpha-1 antitrypsin. Ki67 staining showed a proliferative index of 1%. The tumour cells were negative for glucagon, calcitonin, insulin, gastrin, CEA, CK7, MUC 1 and MUC 5AC.

The patient made a good recovery post-surgery and was clinically well at the 6 months follow-up.

Case #2

A thirty-four-year-old Caucasian man was admitted as an emergency with right-sided abdominal pain. Clinical examination was unremarkable. Laboratory analysis showed an elevated lipase level of 1375 U/L (normal range:0-67 U/L) and a slightly increased white cell count.

CT revealed an enhancing mass in the second part of duodenum that was obstructing the pancreatic duct and the biliary system (**Figure 3**). An oesophago-gastro-duodenoscopy showed a sub-mucosal mass in the first part of duodenum, away from the ampulla. Subsequent EUS suggested a gastrointestinal stromal tumour arising from the ampulla and dilated common bile duct. However, FNA was highly suggestive of a well differentiated NET. The patient underwent a pylorus-preserving pancreatico-duodenectomy.

Pathological examination (**Figure 4**) revealed a well circumscribed tumour within the wall of the second part of the duodenum measuring 20mm in diameter. Histologically this was composed of large cells with abundant, granular, eosinophilic cytoplasm and relatively small nuclei with coarse, stippled chromatin. The predominant architectural pattern was nested in type with trabecular areas present focally. Numerous psammoma bodies were also seen. Mitotic activity could not be demonstrated (formal count 0 in ten high power fields). Vascular and perineural invasion were not evident. None of the 11 lymph nodes harvested contained any metastatic tumour.

The tumour showed positive immunohistochemical staining for synaptophysin, chromogranin A, CD56 and PGP 9.5. Insulin and glucagon were both negative. Proliferative index by Ki67 was less than 1%.

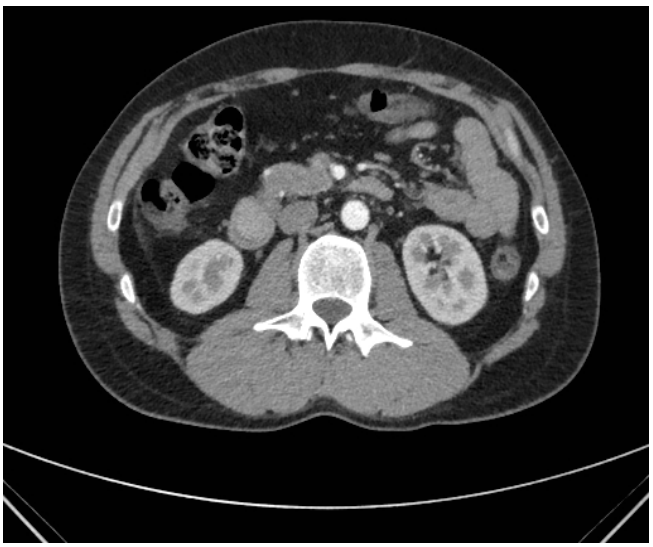

Figure 3. Pre-operative CT of the abdomen demonstrating a large mass arising from the second part of the duodenum.

The patient made a good recovery and was clinically well at 6 months follow up.

DISCUSSION

PNETs consist of a heterogenous group of neoplasms that present a significant clinical challenge. All such tumours have malignant potential with the risk of adverse outcome determined by the following pathological features: tumour size; mitotic activity; presence of tumour necrosis; vascular or perineural invasion; and Ki67 index. PNETs have an overall 5-year survival of 93%. In contrast, the 5-year survival for poorly differentiated neuroendocrine carcinomas is typically 22%. PNETs are currently staged and graded separately based on the guidelines adopted by both European and North American NET Societies. In the current 2010 WHO classification system, PNETs are divided into well-differentiated (grades 1 [G1] and 2 [G2]) and poorly differentiated (G3) neuroendocrine carcinoma [5].

More than 90% of all duodenal NETs arise in the first and second part of the duodenum and approximately 20% occur in the peri-ampullary region. Most duodenal NETs are T1 but regional lymph node metastases have been reported to occur in 40-60% of cases. Ampullary or peri-ampullary tumours may have a more aggressive behaviour and different pathological expression [6].

The grading of NETs is based on the mitotic count (G1: <2 mitoses/10 high power fields (HPF), G2: 2-20 mitoses/10 HPF, G3: >40/10 HPF) and Ki-67 index (G1: Ki-67 index of <3%, G2: Ki-67 index of 3-20%, G3: Ki-67 index >55%) [5].

Based on clinical presentation, NETs were historically separated into two categories: functional *versus* non-functional, according to the symptoms caused by the hormone the tumours secrete into the bloodstream. Non-functional NETs are often diagnosed late as they usually become clinically apparent due to tumour compression or invasion of extra-pancreatic organs or present with distant metastases.

Imaging techniques used for detecting NETs include CT, magnetic resonance imaging, EUS, somatostatin receptor scintigraphy, and positron emission tomography [7]. EUS-guided FNA has become the accepted standard of practice for the detection, diagnosis and staging of PNETs [8]. In our unit, all patients are investigated with a staging CT of the chest, abdomen and pelvis, and EUS with FNA. In cases with diagnostic uncertainty, an octreotide or MIBG scan is performed prior to surgery. Blood tests include: chromogranin A, synaptophysin and/or neuron-specific enolase. Elevated plasma chromogranin A levels have been associated with poor overall prognosis in patients with NETs.

PNETs have a wide morphologic repertoire including oncocytic, pleomorphic, ductulo-insular and lipid-rich variants. An oncocytic variant of PNET is rare, with a limited number of cases reported in the literature. These tumours are characterised by abundant eosinophilic granular cytoplasm, finely granular chromatin, and relatively smooth nuclear membrane. Additional features include rare isolated cells. In contrast to typical PNETs, tumour cells are larger and more cohesive. Prominent nucleoli are commonly noticed. The oncocytic variant of PNETs and pancreatic ductal adenocarcinoma have overlapping cytomorphological features such as clusters of disorganized cells, nuclear crowding, prominent nucleoli and nuclear size variation. Chen *et al.* reported three cases of the oncocytic variant of PNETs which were misdiagnosed by FNA as pancreatic ductal adenocarcinoma (n=2) or suspicious for carcinoma (n=1) [9]. Unlike other morphologic variants, the oncocytic PNETs have been found to be more aggressive in some studies. It is extremely difficult to differentiate the oncocytic variant preoperatively, and diagnosis is achieved only on histological examination.

It is generally agreed that, if possible, all functioning PNETs should be resected, with the exception of patients with multiple endocrine neoplasia type 1 (the role of surgery remains controversial because patients often have multifocal disease) or those with small (<2cm) non-functioning PNETs. For incidental PNETs that are <1 cm, it is reasonable to consider a "watch and wait" approach. For larger tumours that are resectable, surgery is indicated [10].

Options for resection of small periampullary NETs include pancreatico-duodenectomy, trans-duodenal local resection or endoscopic resection. Endoscopic resection can only be considered in cases of small tumours that are not involving the ampulla, pancreatic and biliary ducts.

Conclusion

Oncocytic variant of NET is rare and its diagnosis can be challenging. The lack of specific clinical features makes preoperative diagnosis difficult. Although there is limited number of cases, based on the current literature, the prognosis of this variant is better.

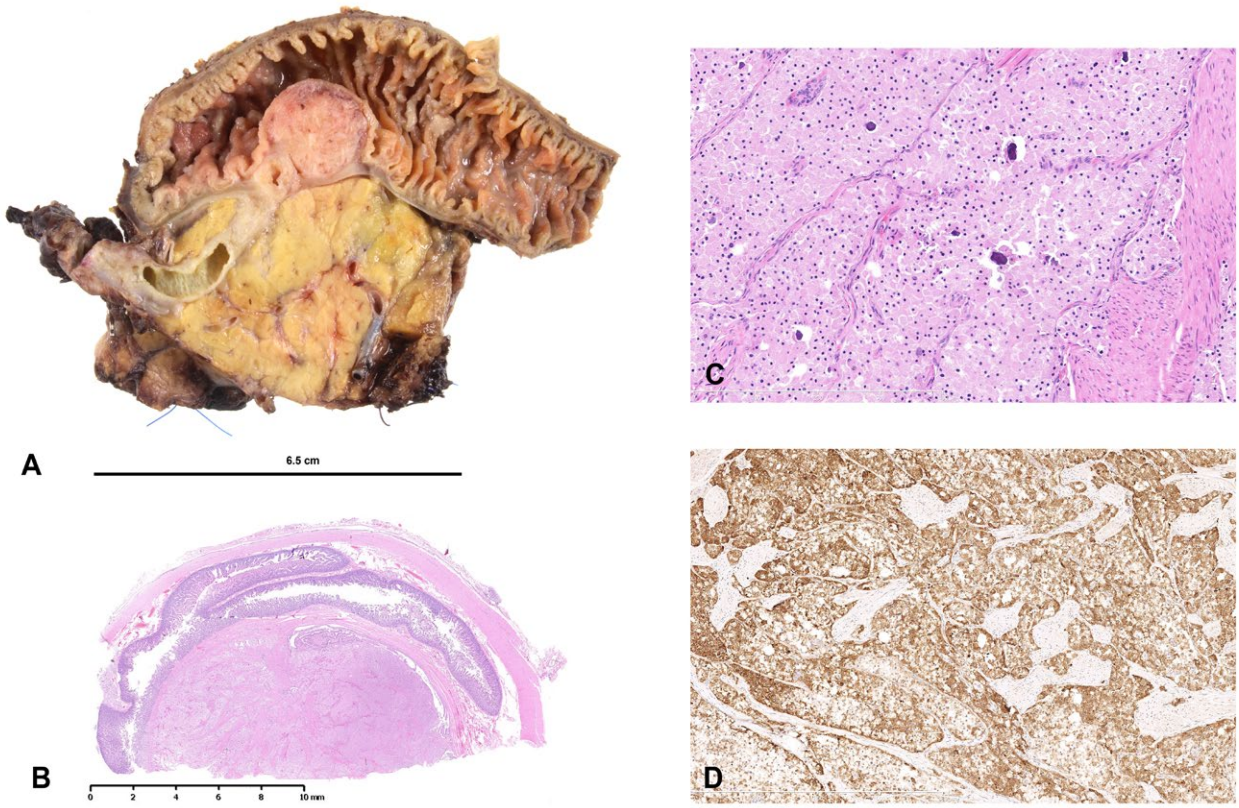

Figure 4. a. Gross appearance of intramural duodenal tumour, **b.** Well circumscribed tumour H&E, original magnification), **c.** Nests of oncocytic tumour cells (H&E, x5), **d.** Positive immunostaining for synaptophysin (x5).

Conflicting Interest

The authors had no conflicts of interest

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