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Case Study

Non-Functioning Pancreatic Neuroendocrine Tumours – Report of an Unusual Case

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Summary

1. Obstructive jaundice is always a matter of concern, and will often imply either a biliary stone or a pancreatic lesion. Cross-sectional imaging is mandatory.
2. Most large pancreatic tumours are the highly malignant adenocarcinomas, with a poor outcome in many cases. Pancreatic neuroendocrine tumours (NETs, islet cell tumours) are much more rare, but need to be considered, especially in a younger age group, and seem to be increasing in incidence. Identification of the presence of somatostatin receptors with radionuclide imaging is very helpful, as is described in this case report.
3. Unless these lesions are very small, generally less than 2cm, they are best removed surgically, with retention of as much normal pancreatic tissue as possible to minimise surgical complications and avoid consequential life-long insulin-dependent diabetes.
4. This case illustrates the problem of deciding on the extent of operative removal in the face of other apparently benign-appearing pancreatic lesions, and the necessity for a fine judgement call.
5. Discovery of an islet cell tumour in a young patient, especially in the presence of multiple abnormalities in the pancreas, suggests that genetic screening, particularly for MEN1, should be actively pursued.
6. In spite of such islet cell tumours showing apparently benign grade 1 morphology, there is always the potential for malignant recurrence, and long-term, probably life-long, follow-up is required even in the absence of a clear genetic abnormality.

Abstract

Pancreatic neuroendocrine tumours represent a heterogeneous collection of neoplasms which are relatively rare, but of rising incidence. They are further classified as functioning or non-functioning, according to their secretory behaviour and symptomatology. The more common of the two, non-functioning tumours often remain asymptomatic for a long duration, so many patients present late with metastasis. This case report presents a 25-year old woman with a large 5x4cm non-functioning pancreatic neuroendocrine tumour (NF-pNET), for which she underwent a pylorus-preserving pancreaticoduodenectomy. Unusually young to have such a neoplasm, she also has some atypical clinical features suggestive of an underlying genetic syndrome such as multiple endocrine neoplasia type 1. This case study goes on to discuss the optimal diagnosis and surgical management of NF-pNETs, addressing some questions raised by this unusual case.

Case History

Miss X is a 25 year old woman who presented to A+E with jaundice, severe pruritis, steatorrhoea, and severe bloating. Prior to this, she had been feeling vaguely unwell for a few months, with intermittent irregular bouts of abdominal pain, cramping, flatulence, and loose stools.

Miss X's past medical history includes long-term excessive laxative use, and periods of dependency upon opiate-based medications. Aside from this, she had no other past medical history, and was fit and well prior to the onset of her symptoms. She was not on any regular medication except the unprescribed laxatives, and has no known allergies. Miss X has a family history of cancer in all four grandparents, including cervical cancer, leukaemia, melanoma, and prostate cancer. When well, Miss X works as a community mental health nursing associate. She reports having never smoked or taken recreational drugs, and rarely drinks alcohol. She lives with her parents, and has no dependents. Systems review revealed that Miss X had experienced bouts of vomiting a few days before going to A+E, along with some tar-like stools before the steatorrhoea developed. She had also encountered long-standing fatigue for the past few months, which she felt had been somewhat overlooked at multiple GP consultations. At the same time as she developed jaundice, she also noticed significant unexplained bruising on her limbs.

On examination, Miss X was visibly jaundiced, with bruising and excoriations on her arms and legs. Her abdomen was soft but tender, with some guarding. Bowel sounds were present. Miss X's bilirubin was significantly increased, reaching a peak of 118 umol/L. Her alanine aminotransferase levels were measured as 340 Int Unit/L, and her alkaline phosphatase grossly elevated to 1102 Int Unit/L. In the context of her clinical presentation, this was suggestive of obstructive jaundice.

CT and MRI scans revealed a 53 x 42 x 45 mm

mass in the head of pancreas causing proximal biliary obstruction, with consequent dilatation of the biliary tree. No vascular invasion was seen. Furthermore, multiple cysts were noted in the body and tail of the pancreas, and both kidneys, in addition to a right adnexal cyst. Some small peribronchial nodules (<1cm) were also seen in the right lower lobe of her lung. Given the history and context of this case, the mass in the pancreatic head was deemed a suspected neuroendocrine tumour (NET). Miss X subsequently underwent an ^{111}in-octreotide scan, to verify the nature of the tumour, and to check for any other potential neuroendocrine tumours (NETs) in her body. Her calcium and parathyroid hormone levels were normal.

Miss X underwent a pylorus-conserving pancreaticoduodenectomy, from which she recovered relatively swiftly. A total pancreatectomy was decided against, with the reasoning that the cysts in the pancreas body and tail looked benign and fluid-filled. She will have regular radiological imaging, with a view to intervene if required in the future.

The pathology report identified the pancreatic neoplasm as a G2 intermediate well-differentiated NET. Given her young age and numerous multi-organ cysts, there is a possibility that an underlying genetic syndrome such as multiple endocrine neoplasia type 1, or von Hippel-Lindau could be driving her phenotype. Miss X has since been referred for genetic testing, with results yet to come.

Background

Pancreatic neuroendocrine tumours (pNETs) are a rare subset of pancreatic neoplasms which originate from pancreatic islet cells. Much rarer than pancreatic adenocarcinomas, they represent just 1-2% of total pancreatic malignancies[1], although their incidence is rising[2]. In the population, their incidence peaks in the 5th decade[2], with a slight male preponderance[1]. pNETs may be classified as functioning, or non-functioning, depending on their ability to secrete active hormones and the symptomatology they elicit. Insulinomas and gastrinomas are examples of functioning-pNETs, which manifest with consequences of their respective excess hormone secretion. Non-functioning pNETs (NF-pNETs) can be further subdivided into three types: those that secrete no hormones, those that secrete hormones at a level insufficient to elicit symptoms, and those that secrete hormones that do not cause symptoms, such as chromogranin A, pancreatic polypeptide, ghrelin, neurotensin or calcitonin[3].

Unlike functioning pNETs, NF-pNETs typically have an indolent natural history. They are often an incidental discovery on imaging, or remain undetected until they reach a tumour burden sufficient to elicit a mass effect or seed metastases. Large tumours may cause local compressive effects, including jaundice, abdominal pain, nausea, weight loss, and more. Conversely, many patients will remain asymptomatic, and eventual detection of their NF-pNET is an incidental finding on a scan for another indication. Consequently, NF-pNETs have a worse prognosis than pNETs, as many patients already have metastases at first presentation, which are commonly hepatic.

The role of genetics

A striking feature of this case report is the patient's young age. A recent study following nearly 5000 patients with NF-pNETs found the median age of diagnosis to be 59 years[2], and yet Miss X was just 25 years old on initial presentation. This, combined with the identification of multifocal cysts throughout the pancreas, in both kidneys, and the uterus adnexa, strongly merits consideration of an underlying genetic predisposition to tumour development. Sporadic pNETs tend to present at a later age[4], and are typically solitary lesions[5].

Genetic analysis plays a significant role in the aetiology of some pNETs; around 10-15% of cases are associated with an underlying syndrome such as multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis type 1, or tuberous sclerosis[6]. Listed in order of relative frequency[7], these syndromes all exhibit autosomal dominant inheritance, and are driven by aberrant or absent tumour suppressor genes.

MEN1-associated pNETs typically differ from sporadic pNETs by having a younger age at diagnosis, multi-focality within the pancreas, and concomitant tumours in other organs[8]. They often initially present as multiple microadenomas, with a larger tumour that has flagged investigations in the first place[9]. VHL patients also have a propensity to develop multifocal pancreatic cysts, in addition to NF-pNETs. Despite her lack of relevant family history, these syndromes can arise de novo, and both warrant testing in Miss X. However, the majority of NF-pNETs are not associated with an underlying genetic cause[10].

Diagnosing NF-pNETs

A key issue concerning NF-pNETs is their difficulty of diagnosis at an early stage, attributable largely to their indolent nature, slow growth, and lack of initial symptomatology[11]. This, combined with the fact that NF-pNET incidence is increasing[2], highlights a need for improved diagnostic methods, to identify these neoplasms before metastasis. That being said, this could be challenging due to their tendency to presenting late, or as an incidental finding. Miss X did experience several months of vague, non-specific symptoms prior to coming to hospital, but given her age and unremarkable family history, a pancreatic neoplasm was unlikely to be high on a list of differential diagnoses.

Present European guidelines state that diagnostics for NF-pNETs should include a multimodal approach, including biochemical tests, imaging, and pathology, as well as genetic testing if indicated[12]. Chromogranin A (CgA) and pancreatic polypeptide are both recommended as circulating tumour markers in the UK guidelines[13], although the former has been deemed the best marker for NETs. Plasma CgA is elevated in both functioning and non-functioning pNETs, and successful treatment is associated with a decrease in circulating levels[14]. As a point of caution, proton pump inhibitors can artificially elevate CgA levels, but following drug cessation levels normalise[14]. Chronic renal insufficiency and liver failure also falsely elevate levels[15]. Alternatively, pancreatic polypeptide has been found to have a specificity of 84% when used for surveillance[16]. A serum calcium and parathyroid level screen should be performed in patients with suspected MEN1, as primary hyperparathyroidism is one of the earliest (but not always the first) endocrine expressions of this condition[17].

European guidelines also advise that several imaging modalities should be used for detecting and locating primary tumours, including computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SSRS)[12]. CT has good sensitivity and specificity; with contrast, pNETs appear as hyperenhancing well-circumscribed lesions. The evidence suggests that the presence of calcification within these tumours and

hypoenhancement on arterial phase imaging is associated with higher grade, more aggressive tumours, and worse prognosis[18,19]. For detecting smaller pancreatic lesions and liver metastases, however, MRI may have greater sensitivity[20,21]. The role of ultrasound in pNET diagnostics is limited, although endoscopic ultrasound in concert with fine needle aspiration is a useful diagnostic method for identifying lesions and confirming their histopathology[22].

SSRS is a functional modality that uses radiolabelled somatostatin analogues such as ^{111}in-octreotate to check for unknown sites of metastasis[23], although in many centres it has been superseded by functional imaging using a newer radiolabelled tracer, ^{68}Gallium-dotatate positron emission tomography (PET)/CT. This is a sensitive imaging modality recommended as the gold standard for localising and staging pNETs[13]; across various studies it has demonstrated a sensitivity and specificity in the range of 86-100% and 79-100% respectively[13]. One study found that use of 68(Ga) DOTANOC PET/CT altered the management and/or stage in 55% of NET cases[24], showing the clinical utility of this scan type. Generally speaking, well-differentiated (G1-2) tumours show up positive on octreotide scans, and are negative on ^{18}fluorodeoxyglucose-PET, with the converse true for poorly-differentiated tumours (G3+)25.

Surgical Strategies for NF-pNETs

The optimum management strategy of any NF-pNET should naturally be considered and individualised on a case-by-case basis, considering the patient's wishes, fitness for surgery, tumour grade and stage, genetic status, and other significant factors. Generally, surgery is the mainstay of treatment, and remains the only curative option. One study looking at patients with localised, regional and metastatic disease showed that of 425 candidates recommended for surgery, those who underwent resection had a median survival difference of 114 months, compared to 35 months for those who opted against surgery[26]. One could argue any study comparing mortality of resected to non-resected patients is at large risk of selection bias, but Hill and colleagues attempt to control for this by comparing resected patients with those who were recommended, but did not undergo, resection. Reasons for not undergoing surgery were withheld from the authors, and could remain a potential confounder.

While guidelines for sporadic NF-pNETs are well-defined[12], the optimal surgical management for MEN1-associated pNETs possesses some areas of controversy[27]. Although we have not yet had verification regarding Miss X's genetic status, this remains an interesting point of discussion for this report. A consensus seems to exist that for MEN1-associated NF-pNETs over 2cm in size, surgical resection is indicated. However, there is debate regarding 'small' MEN1 NF-pNETs, classified as 2cm and under. There is a strong argument for surveillance, as some data suggests that 50-80% of these lesions exhibit stable behaviour[27]. Similarly, for sporadic asymptomatic NF-pNETs <2cm the European guidelines recommend surveillance, providing the pNET is well-differentiated (G1/G2)[12].

However, recent research suggests that MEN1-associated NF-pNETs, irrespective of tumour size, can demonstrate unpredictable malignant behaviour[27], suggesting surgical resection should be considered no matter the size. One prospective study looked at the long-term follow up of MEN1 patients with 'small' NF-pNETs (<2cm) who did not qualify for surgery, and found 39% of patients went on to exhibit progressive disease[28]. Miss X's primary NF-pNET far surpassed the 2cm threshold, so surgery was clearly indicated irrespective of her MEN1 status, but this highlights an interesting area of debate nonetheless.

One interesting question this particular case raises is whether Miss X should have had a total pancreatectomy instead of a pylorus-preserving pancreaticoduodenectomy (excising the head of pancreas), given the presence of cystic lesions throughout the pancreas body and tail. On the one hand, the imaging report described the cysts as 'benign and fluid-filled' – should these lesions indeed remain non-malignant, it would be favourable to leave the non-cancerous pancreas behind, to retain some endogenous exocrine and endocrine function.

Total pancreatectomy has historically been associated with a higher mortality and morbidity than pancreaticoduodenectomy[29]; development of diabetes mellitus is virtually inevitable, and patients often suffer with delayed gastric emptying. Pylorus-preserving pancreaticoduodenectomy reduces the likelihood of these complications, although anastomotic leaks, pancreatic fistulae, malabsorption, cachexia, and diarrhoea remain risks of both procedures, alongside other non-specific complications of abdominal surgery[30]. One study found total pancreatectomy to have an 8% 30-day post-operative mortality compared to 1.5% for pancreaticoduodenectomy[31]. If the cysts are just a benign abnormality, it would seem that the pancreaticoduodenectomy was the logical option, with fewer risks.

On the other hand, one could argue that all such lesions have malignant potential until proven otherwise. In the case of Miss X, a 'watch and wait' approach has been taken with the remaining pancreatic cysts, using regular radiological surveillance to check for any changes in their behaviour. However, should they become malignant, Miss X would once again be subjected to major surgery, with many of the same risks and complications as before, and causing further disruption to her life. The probability of these cysts being a premalignant precursor lesion perhaps should be histologically evaluated before proceeding with surgery, if possible. I was unable to find evidence of histology being performed on Miss X's cysts; perhaps this is one way in which her care could have been theoretically improved.

The cysts could merely represent a non-neoplastic abnormality, but there is also a chance they could be a mucinous precursor lesion, such as a mucinous cystic neoplasm (MCN). Found most often in the body and tail of the pancreas, with a 9:1 female preponderance, MCNs are fluid-filled cysts, that can grow up to 3cm or larger in size[32]. MCNs can follow a molecular progression from cystadenoma to carcinoma and invasion, and KRAS2 mutations are thought to often play a role in this progression[33]. Approximately one third of MCNs exhibit invasive behaviour[34]; resection is thus recommended, as many lesions are expected to progress to carcinoma within the lifespan of the individual[35]. The difficulty lies in differentiating non-neoplastic cysts from mucinous precursor lesions such as MCNs, and identifying the risk of progression of mucinous precursors to actual invasive carcinoma.

One study showed that site and size of cysts within the pancreas actually offers no correlation with malignant potential[36]. While CT-guided fine needle aspiration (CT-FNA) has shown a sensitivity of 98% in detecting malignancy in solid pancreatic masses, this figure falls to 62% for cystic aspirates, possibly due to hypocellularity of the sample[37]. However, analysing cystic fluid for tumour markers such as CA 19-937 and carcinoembryonic antigen[38]

(CEA) may help identify mucinous precursors. More work needs to be done to unravel the molecular signatures of premalignant lesions, in order to help assess risk and necessity for excision.

Enucleation is also an option for small low-grade pancreatic lesions, providing the integrity of the pancreatic duct can be conserved[39]. A relatively recent technique, it is indicated for cystic lesions and pNETs, and has been associated with lower rates of post-operative complications than a regular pancreatectomy. Long-term prognosis appears similar between the two[40,41]. While Miss X would have had the pancreaticoduodenectomy regardless, due to the large mass in the pancreas head, perhaps the other smaller lesions could theoretically have been enucleated to reduce risk of future malignancy, while retaining some of her pancreas. However, this may have been too complex a procedure, and I was unable to find any literature concerning the use of these two techniques in concert.

Future Perspectives

While surgical resection is currently the mainstay of treatment for these neoplasms, this is often limited in cases of metastatic disease. Moreover, resection is associated with significant morbidity, as discussed previously. There is thus an unfulfilled need for anti-proliferative medical therapies, be it to delay or even halt tumour growth. Conventional chemotherapy does not play a prominent role in the treatment of pNETs; there are very few randomised control trials looking at the use of chemotherapy for NETs. Streptozotocin-based combination regimens may offer some value for moderately differentiated pNETs, but at present there remains insufficient evidence to support use of adjuvant systemic treatment following surgical resection of pNETs[42]. More recently, targeted therapies such as somatostatin analogues have been subject to research. In patients with advanced metastatic pNETs, the analogue lanreotide has been shown to reduce disease progression and prolong progression-free survival[43]. Other targeted therapies include the tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus, which have showed encouraging phase III results[44,45]. However, a greater understanding of NF-pNET tumour biology and potential drug targets is ultimately still needed, for therapeutic agents remain a great unmet need in the management of neuroendocrine tumours.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented for the publication of this case study.

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