Pancreatic endocrine neoplasia: familial syndromes

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Abstract

While the vast majority of pancreatic neuroendocrine tumours (pNETs) are sporadic, the recognition of an inherited pNET represents an evolving clinical responsibility of practising pathologists in the era of personalized medicine. The initially well-defined inherited pNET syndromes includes multiple endocrine neoplasia type 1 (MEN-1), von Hippel Lindau disease (VHL), neurofibromatosis type 1 (NF) and tuberous sclerosis (TS). Over the past decade, the spectrum of inherited pNETs has been expanded by the inclusion of new presentations such as multiple endocrine neoplasia type 4 (MEN-4), glucagon cell adenomatosis (Mahvash disease) along with germline mutations in DNA repair genes (*MUTYH*, *BRCA2*, and *CHEK2*) in a subset of seemingly sporadic looking pNETs as well as isolated case reports of succinate dehydrogenase deficient (SDH)- and mismatch repair deficient-pNETs occurring in the setting of *SDH*-related familial paraganglioma syndrome and Lynch syndrome, respectively. The findings have pointed out that the spectrum of inherited pNETs is indeed larger than what most physicians generally anticipate, likely reaching a rate greater than 15% of the overall presentations. From a morphological perspective, the identification of multifocal pNET should prompt the attention of pathologists to the possibility of an underlying genetic susceptibility. Since not all inherited pNETs manifest with multifocal disease, careful morphological assessment of the tumour and the non-tumorous pancreas, and application of immunohistochemical biomarkers are essential in the prediction of inherited pNETs. In order to facilitate the recognition of inherited pNETs, this review is aimed to provide a practical overview of pancreatic endocrine manifestations of MEN-1, MEN-4, VHL, NF-1, TS and glucagon cell adenomatosis.

Keywords glucagon cell adenomatosis; inherited pancreatic neuroendocrine tumours; lynch syndrome; multiple endocrine neoplasia type 1; multiple endocrine neoplasia type 4*MUTYH*; neurofibromatosis type 1; succinate dehydrogenase; tuberous sclerosis; von Hippel-Lindau disease

Introduction

Neuroendocrine neoplasms in general, and certainly those arising in the pancreas, are usually sporadic in origin. However, there is a well-characterized subset that falls within the remit of "familial neuroendocrine tumours". The initially well-defined four familial or inherited scenarios in which pancreatic neuroendocrine tumours (pNETs) are encountered include multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF-1) and tuberous sclerosis (TS).[1–6]

In addition to rare familial cases of insulin-producing pNETs,[7] the spectrum of inherited pNETs has been expanded over the past decade with the inclusion of novel presentations including multiple endocrine neoplasia type 4 (MEN-4)[6,8] and glucagon cell adenomatosis (GCA; also known as Mahvash disease).[9–11] Furthermore, a recent study of whole-genome sequencing of seemingly sporadic pNETs identified previously unreported germline mutations in the DNA repair genes including *MUTYH*, *CHECK2* and *BRCA2*.[12] Together with germline mutations in *VHL* and *MEN1* genes, that particular study found a frequency of 17% of germline mutations in seemingly sporadic pNETs.[12] The advent of screening modalities in patients with familial syndromes also unrevealed a link between a mismatch repair protein (MMR)-deficient pNET and Lynch syndrome.[13] In addition, a succinate dehydrogenase deficient (SDH)-pNET was also reported in a patient with germline *SDHD* mutation in the context of familial paraganglioma syndrome.[14]

These findings have helped us to better understand the spectrum of inherited pNETs is larger than what physicians often anticipate. As a result, the distinction of an inherited pNET by providing insight to facilitate genetic triaging represents an evolving clinical responsibility of practising pathologists in the era of personalized medicine. From a morphological perspective, the identification of multifocal pNETs should prompt the attention of pathologists to the possibility of an underlying genetic susceptibility. Since not all inherited pNETs manifest with multifocal disease, careful morphological assessment of the pNET and the non-tumorous pancreas, and application of immunohistochemical biomarkers are helpful in the prediction of inherited pNETs.[15–17] This review is aimed to provide a practical overview of pancreatic endocrine manifestations of MEN-1, MEN-4, VHL, NF-1, TS and GCA.

Multiple endocrine neoplasia syndrome type 1

This is an autosomal dominant condition, with affected individuals displaying 94% penetrance and manifestation of the associated pathology by the age of 50 years.[18] These patients have germline mutations of the *MEN-1* tumour suppressor gene located on chromosome 11q13 and consequent loss of a 610 amino acid nuclear protein, menin, that primarily suppresses cell proliferation.[2,8,11,19] Hereditary pNETs are encountered in up to 75% of patients with MEN-1.[19] Primary hyperparathyroidism usually manifests before pancreatic neuroendocrine lesions.[20] Most MEN-1 patients present with Zollinger-Ellison syndrome due an autonomous gastrin-secretion by a multifocal NET. However, it is worth remembering that in MEN-1, duodenal gastrin-producing tumours are significantly more common than those arising in the pancreas.[2,11] Recent observations suggested that the occurrence of gastrin-producing pNET is extremely rare in patients with MEN-1 syndrome. Thus, the most common

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functional presentation of MEN-1 related pNET is currently linked to insulin producing pNETs (insulinomas). In contrast to sporadic pNETs, those associated with MEN-1 tend to present at an earlier age (30–50 years), have a higher rate of post-operative recurrence and are a common cause of death in these patients.[21]

The hallmark of MEN-1 related pancreatic endocrine manifestations is the presence of multifocal and/or unifocal pNET arising in the background of precursor proliferations (islet dysplasia, microadenomatosis, ductulo-insular complexes or nesidioblastosis) and peliosis of the non-tumorous islets.[2,6,22] Initially thought to be highly specific to MEN-1, the vast majority of these precursor proliferations have now been recognized in patients with VHL and GCA.[4,9–11]

Dysplastic islets are defined as normal-sized or slightly enlarged islets containing neuroendocrine cells displaying mild cytological atypia, arranged in trabeculae that show loss of the normal spatial and quantitative arrangement of the four main cell types (alpha-, beta-, delta-, and gamma-cells) (Figures 1 and 2).[2,6,15,22] Therefore, careful examination of the non-tumorous pancreas with immunohistochemistry for glucagon (alpha-cells), insulin (beta-cells), somatostatin (delta-cells), and pancreatic polypeptide (gamma-cells) is required to detect islet dysplasia in all patients with pNETs (Figure 2). Once islet dysplasia attains a size of 0.5 mm, it is called microadenoma or neuroendocrine microtumour (microNET) (Figure 3).[2,6,22] A microadenoma that exceeds a size of 5 mm is termed pNET.[2] In addition to solitary or multifocal pNET, multiple small, often non-functioning microadenomas (diffuse microadenomatosis) in association with foci of ductulo-insular complexes (nesidioblastosis) are characteristics of MEN-1 pancreata (Figures 4 and 5).[2,6,22]

Histologically, the microadenomas are characterized by a trabecular or mixed trabecular solid growth pattern and the stroma is typically dense and sclerotic (Figure 3). Most MEN-1-related pNETs are well-differentiated neuroendocrine neoplasms (Grade 1 or Grade 2 pNETs). Among inherited pNETs, plurihormal immunohistochemical expression profile is considered a distinct feature of MEN-1.[11,17] Immunohistochemically, glucagon is the most frequently detected pancreatic hormones followed by pancreatic polypeptide, insulin, and somatostatin (Figure 6).[11,17] Cystic change is frequently correlated with glucagon-producing pNETs in MEN-1.[23] While around 40% of sporadic pNETs can harbour somatic *MEN-1* mutation,[12] immunohistochemical loss of menin (protein encoded by *MEN-1* gene) (Figure 7) may be a harbinger of MEN-1 syndrome especially in the background of multifocal disease or precursor proliferations in association with pNETs.[15,17]

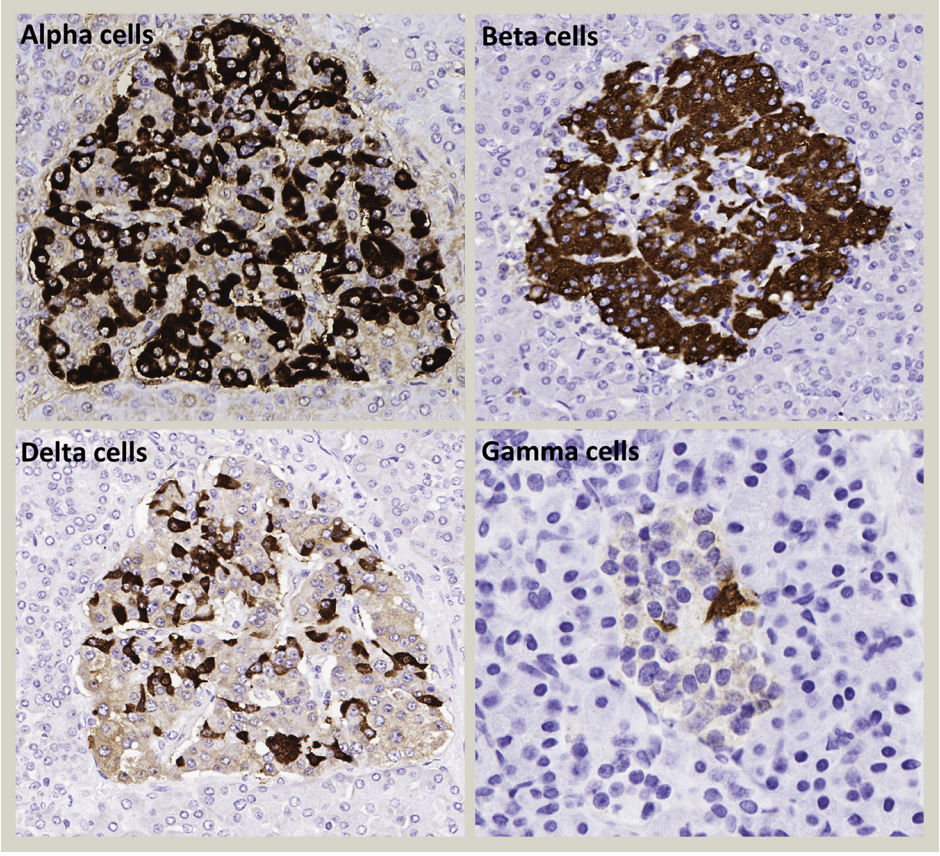

Figure 1 Normal distribution of the four pancreatic neuroendocrine cells is illustrated in this photomicrograph. Alpha cells typically line the outer tubules (glucagon) and surround the inner tubules containing beta-cells (insulin). Both delta (somatostatin) and gamma cells (pancreatic polypeptide) display a random distribution. It is important to note that gamma cells are more populated in the head of pancreas. One might see absence of gamma cells in some islets located in the tail of the pancreas.