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Secrete and Exude-Pancreatic Neuroendocrine Tumour

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Abstract

Pancreatic neuroendocrine tumour is derived from neuroendocrine cells of pancreas or hormone secreting cells within vicinity of pancreas and is categorized into indolent well differentiated neuroendocrine tumour (WDNET) and the aggressive, rapidly progressive poorly differentiated neuroendocrine carcinoma(PDNEC). Well differentiated neuroendocrine tumour (WDNET) demonstrates inactivation of MEN1, genetic mutation or loss of DAXX / ATRX, altered mTOR pathway, incrimination of PTEN, TSC2, PIK3CA genes with alteration of VHL. Poorly differentiated neuroendocrine carcinoma and mixed neuroendocrine / non neuroendocrine neoplasm delineates alterations within TP53, RB, KRAS, APC, BRAF or SMAD4 / DPC4 genes. Neuroendocrine tumour delineates an organoid architecture with solid nests, trabeculae, gyri, cords, festoons, ribbons, glandular, pseudo-acinar or tubulo-acinar articulations. Miniature to intermediate tumour cells are permeated with eosinophilic, amphophilic, finely granular cytoplasm, centric, spherical to elliptical, uniform nuclei with finely stippled 'salt and pepper' nuclear chromatin, inconspicuous nucleoli and an abundant circumscribing vascular network. Pancreatic neuroendocrine tumour is immune reactive to CK8 / CK18, CAM 5.2, OSCAR, AE1 / AE3, synaptophysin, chromogranin A, INSM1, CD56, neuron specific enolase (NSE) or CD57. Pancreatic neuroendocrine tumour pancreas requires segregation from neoplasms such as acinar cell carcinoma, pancreatoblastoma, solid pseudo-papillary neoplasm, pancreatic ductal adenocarcinoma, paraganglioma, clear cell tumours as clear cell sarcoma, metastatic renal cell carcinoma, PEComa or solid variant of serous cystadenoma. Comprehensive surgical eradication is recommended for treating well differentiated neuroendocrine tumour. Poorly differentiated neuroendocrine tumour is appropriately treated with platinum based chemotherapy.

Keywords: Pancreas; Neuroendocrine; Organoid; Tumour

Abbreviations: WDNET: Well Differentiated Neuroendocrine Tumour; PDNEC: Poorly Differentiated Neuroendocrine Carcinoma; MINEN: Mixed Neuroendocrine Non Neuroendocrine Neoplasms; WHO: World Health Organization.

Introduction

Pancreatic neuroendocrine tumour is a neoplasm derived from neuroendocrine cells of pancreas or hormone secreting cells occurring within vicinity of pancreas. Tumefaction is comprised of variants as the indolent well differentiated neuroendocrine tumour (WDNET) with prolonged clinical course and rapidly progressive poorly differentiated neuroendocrine carcinoma (PDNEC) with an aggressive clinical course. Neoplasms appear immune reactive to diverse neuroendocrine markers as synaptophysin and chromogranin A. Besides, mixed neuroendocrine non neuroendocrine neoplasms (MiNEN) are constituted of admixed neuroendocrine and non-

neuroendocrine component as adenocarcinoma or acinar cell carcinoma wherein individual component configures ≥ 30% of neoplasm. Generally, functional tumours are associated with elevated serum hormone levels and an accompanying clinical hormonal syndrome. Frequently discerned nonfunctional tumours appear un-associated with clinical hormonal syndrome. Nevertheless, neoplasm may be associated with elevated serum hormone levels or tissue hormones as enunciated upon cogent immunohistochemistry. Nonfunctional tumour < 0.5 centimetre magnitude is denominated as pancreatic neuroendocrine micro-adenoma.

Pancreatic neuroendocrine tumour was previously denominated as islet cell tumour, islet cell carcinoma, carcinoid or APUDoma.

Pancreatic neuroendocrine tumour configures 1% to 5% of pancreatic neoplasms. Tumefaction is commonly discerned within third decade to sixth decade although no age of disease emergence is exempt. An equivalent gender predisposition is observed [1,2]. Majority of neoplasms occur as sporadic lesions although 10% to 20% tumours are associated with distinctive syndromes. Around 20% to 70% of multiple endocrine neoplasia1(MEN1), 20% of von Hippel-Lindau (VHL), 10% of neurofibromatosis type1(NF1) or 1% of tuberous sclerosis complex (TSC) appear concordant to pancreatic neuroendocrine tumour.

Well differentiated pancreatic neuroendocrine tumour (WDNET) is frequently confined to tailor body of pancreas whereas poorly differentiated neuroendocrine carcinoma is encountered within head of pancreas.

Of variable aetiology with concurrent, pertinent clinical syndrome, pancreatic neuroendocrine tumour is posited to arise due to cogent risk factors as cigarette smoking, diabetes mellitus or a first degree relative with history of carcinoma [1,2].

A subset of neoplasms is associated with multiple endocrine neoplasia 1(MEN1) with configuration of MEN1 gene upon chromosome 11q13, von Hippel-Lindau syndrome with VHL tumour suppressor gene situated upon chromosome 3p25, neurofibromatosis 1(NF1) with microdeletion within neurofibromin gene upon chromosome 17q11.2 or tuberous sclerosis complex with TSC1 tumour suppressor gene confined to chromosome 9q34 or TSC2 tumour suppressor gene confined to chromosome 16p13.3.

Well differentiated neuroendocrine tumour (WDNET) demonstrates inactivation of MEN1 and genetic mutation or loss of DAXX / ATRX. Besides, altered pathway of mTOR with incrimination of PTEN, TSC2, PIK3CA genes may ensue. Besides, genomic alteration of VHL may ensue [2,3]. Poorly differentiated neuroendocrine carcinoma and mixed neuroendocrine / non neuroendocrine neoplasm delineates alterations within TP53, RB, KRAS, APC, BRAF or SMAD4 / DPC4 genes. Pancreatic neuroendocrine tumour delineates pertinent clinical subtypes contingent to diverse cellular components. Incidentally discovered nonfunctional tumours appear enlarged upon presentation. Cogent clinical symptoms as localized obstruction or mass effect may be encountered in neoplasms situated within pancreatic head. Besides, clinical features of multiple endocrine neoplasia1 (MEN1) with micro-adenoma, von Hippel-Lindau(VHL) disease with clear cell tumour, neurofibromatosis(NF1) or tuberous sclerosis complex(TSC) may arise [2,3].

Functioning tumours(10% to 30%) are associated with clinical hormonal syndromes designated as insulinoma is a commonly discerned, indolent, solitary neoplasm <2 centimetre diameter secreting insulin. Whipple triad demonstrates symptoms of hypoglycemia with decimated plasma glucose and alleviation of symptoms upon administration of glucose. Around 5% to 10% neoplasms are multiple and appear as a component of multiple endocrine neoplasia1(MEN1). •gastrinoma is a frequent, functioning pancreatic neuroendocrine tumour which secretes gastrin. The neoplasm exemplifies Zollinger-Ellison syndrome constituted of peptic ulcer or duodenal ulcer, gastroesophageal reflux and diarrhoea. Tumefaction is situated within gastrinoma triangle circumscribed by common bile duct, duodenum and head of pancreas. Tumefaction is predominantly confined to duodenum wherein 20% to 30% tumours are associated with multiple endocrine neoplasia1 (MEN1) [2,3].

Glucagonoma enunciates symptoms of diabetes mellitus, dermatitis as necrolytic migratory erythema, deep vein thrombosis or depression. The solitary, enlarged neoplasm is preponderantly encountered within tail of pancreas. Around > 50% neoplasms appear metastatic upon initial disease representation. Vasoactive intestinal peptide tumour(VIPoma) is additionally designated as Verner-Morrison syndrome and exhibits watery diarrhoea, hypokalaemia, achlorhydria or hypochlorhydria. The solitary, enlarged tumour is commonly confined to tail of pancreas.

Somatostatinoma is an extremely exceptional, solitary, enlarged tumour configuring diabetes mellitus, diarrhoea, steatorrhea, anaemia, malabsorption or cholelithiasis. An estimated >50% neoplasms delineate metastasis upon initial disease representation.

Ectopic hormone producing neuroendocrine tumour arises as a solitary, enlarged neoplasm secreting adrenocorticotrophic hormone (ACTH) with occurrence of Cushing's syndrome, serotonin with emergence of atypical

carcinoid syndrome or growth hormone [2,3].

Upon gross examination, tumefaction is well circumscribed, homogeneous and cystic. Variance in tumour hue and consistency is contingent to proportionate tumour vascularity and circumscribing stroma. Neoplastic hue may range from white, pink, tan to brown. Necrotic foci demonstrate a yellowish tinge. Enlarged neoplasms emerge as lobulated and infiltrative lesions. Pigmented, black pancreatic neuroendocrine tumour is pervaded with intracytoplasmic lipfuscin and appears reminiscent of metastatic melanoma. Lipid rich pancreatic neuroendocrine tumour appears yellow and simulates adrenal cortical neoplasia [2,3].

Pancreatic neuroendocrine tumour may invade adjacent fibrous or adipose tissue, diverse organs and enlarged vascular articulations.

Upon cytological examination, well differentiated neuroendocrine tumour exhibits cellular smears comprised of clusters and singular, uniform, miniature or intermediate, spherical or elliptical cells imbued with amphophilic, finely granular cytoplasm with possible detection of neurosecretory granules. Plasmacytoid cells are frequently discerned.

Poorly differentiated neuroendocrine carcinoma is constituted of overtly malignant cells wherein neoplastic cells may configure miniature cells or enlarged cells. Foci of necrosis are encountered [2,3].

Upon microscopy, well differentiated neuroendocrine tumour delineates an organoid architecture and configures solid nests, trabeculae, gyri, cords, festoons, ribbons, glandular, pseudo-acinar or tubulo-acinar articulations. Carcinoma cells emerge as miniature to intermediate cells permeated with eosinophilic, amphophilic and finely granular cytoplasm, centric, spherical to elliptical, uniform nuclei with finely stippled 'salt and pepper' nuclear chromatin and absent or inconspicuous nucleoli. Circumscribing vascular network is abundant.

Insulinoma is associated with deposition of amyloid. Somatostatinoma exhibits psammoma bodies or hyaline globules.

Well differentiated pancreatic neuroendocrine tumour exhibits variants such as clear cell, lipid rich, oncocytic, rhabdoid or pigmented black neuroendocrine neoplasm [2,3].

Poorly differentiated neuroendocrine carcinoma is comprised of diffuse sheets or solid nests of malignant cells demonstrating significant cellular and nuclear atypia. Nuclei are devoid of 'salt and pepper' nuclear chromatin. Mitotic activity is significant and apoptotic bodies appear abundant. Foci of necrosis are frequently discerned (Table 1).

The neoplasm may emerge as a small cell variant with enhanced nucleo-cytoplasmic ratio and hyperchromatic nuclei with nuclear moulding (Figures 1 & 2).

Large cell variant exhibits enlarged cells permeated with moderate to abundant, amphophilic cytoplasm with prominent nucleoli [2,3].

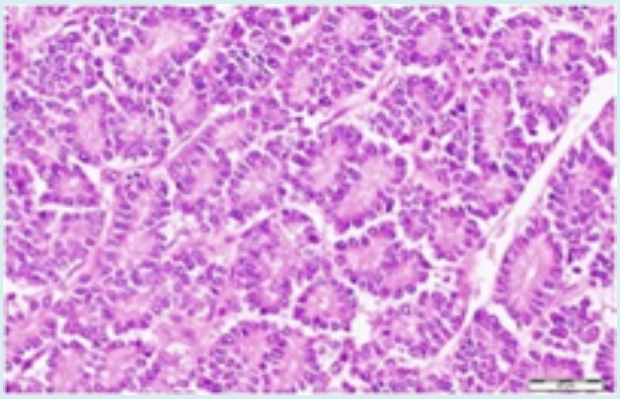

Figure 1: Pancreatic neuroendocrine tumour demonstrating gyri, cords, festoons, glandular articulations and pseudo-acinar structures of neuroendocrine cells with moderate amphophilic cytoplasm, regular nuclei with finely stippled chromatin and inconspicuous nucleoli. Circumscribing stroma is scanty and vascularized [4].

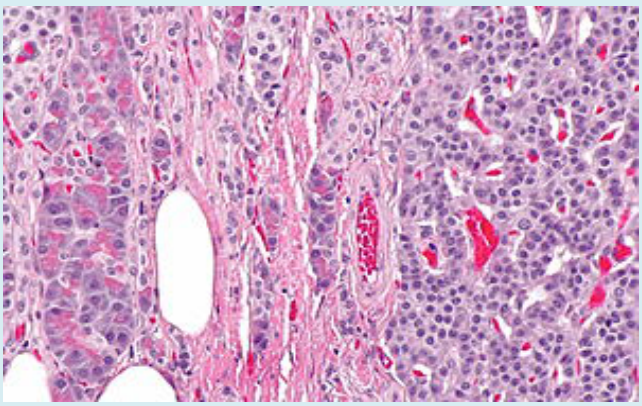

Figure 2: Pancreatic neuroendocrine tumour exhibiting ribbons, nests, cords, glands and pseudo-acinar structures of neuroendocrine cells imbued with moderate eosinophilic cytoplasm, nuclei with finely stippled nuclear chromatin and indistinct nucleoli. Surrounding stroma is vascularized [5].

Grade	Mitosis/10hpf/2 mm^2	Ki67 Proliferative Index
GX	Grade cannot be assessed	
G1	<2	<3%
G2	2 to 20	3% to 20%
G3	>20	>20%

Table 1: Grading of pancreatic neuroendocrine tumour [3,6].

Tumour grade is contingent to Ki67 proliferation index and mitotic count. As per World Health Organization (WHO) classification 2019 and contingent to morphological characteristics, neuroendocrine neoplasm with Ki67 proliferative index > 20% is designated as well differentiated neuroendocrine tumour (WDNET) grade 3 or poorly differentiated neuroendocrine carcinoma (PDNEC).

TNM Classification of Pancreatic Neuroendocrine Tumour

Primary Tumour

TX: Tumour cannot be assessed
T1: Tumour < 2 centimetre magnitude and confined to pancreas
T2: Tumour magnitude > 2 centimetres to < 4 centimetres and confined to pancreas
T3: Tumour magnitude > 4 centimetres and confined to pancreas or tumour invasion into duodenum or bile duct
T4: Tumour extends into gastric region, spleen, colon, adrenal gland or enlarged vascular articulations as wall of celiac axis or superior mesenteric artery.

Regional Lymph Node

NX: Regional lymph nodes cannot be assessed
N0: Regional lymph node metastasis absent
N1: Regional lymph node metastasis present

Distant Metastasis

M0: Distant metastasis absent
M1: Distant metastasis present
M1a: Distant metastasis into hepatic parenchyma
M1b: Distant metastasis into minimally a singular area beyond hepatic parenchyma as pulmonary parenchyma, ovary, non regional lymph nodes, peritoneum or bone
M1c: Localized and distant metastasis present [3,6].

Staging of Pancreatic Neuroendocrine Tumour is Denominated as

Stage I: Tumour is miniature and confined to pancreas with absence of regional lymph node and distant metastasis (T1, N0, M0)

Stage II: Tumour is enlarged with absence of regional lymph node or distant metastasis (T2 or T3, N0, M0).

Stage III: Tumour of variable magnitude with regional lymph node metastasis (any T, N1, M0) OR tumour extends into gastric region, spleen, colon, adrenal gland or enlarged blood vessels as wall of celiac axis or superior mesenteric artery wherein regional lymph node or distant metastasis is absent (T4, N0, M0)

Stage IV: Distant metastasis is present (any T, any N, M1) [3,6].

Pancreatic neuroendocrine tumour is immune reactive to CK8 / CK18, CAM 5.2, OSCAR, AE1 / AE3, synaptophysin, chromogranin A, INSM1, CD56, neuron specific enolase (NSE) or CD57. Occasionally, trypsin may be immune reactive.

Well differentiated neuroendocrine tumour (WDNET) demonstrates an immune reactive panel as Islet1+, PAX6+, TTF1-, CDX2-, SATB2-, somatostatin receptor+ and loss of DAXX / ATRX. Poorly differentiated neuroendocrine carcinoma depicts abnormal expression of p53 and loss of RB1 or SMAD4/DPC4. Immune reactivity to hormones such as insulin, glucagon, gastrin, somatostatin, vasoactive intestinal polypeptide (VIP) or pancreatic polypeptide may be encountered. Pancreatic neuroendocrine tumour is immune non-reactive to beta catenin, trypsin, chymotrypsin or BCL10 [6,7].

Pancreatic neuroendocrine tumour pancreas requires segregation from neoplasms such as acinar cell carcinoma, pancreatoblastoma, solid pseudo-papillary neoplasm, pancreatic ductal adenocarcinoma, paraganglioma, clear cell tumours as clear cell sarcoma, metastatic renal cell carcinoma, PEComa or solid variant of serous cystadenoma.

Functional tumours demonstrate elevated serum hormones, contingent to neoplastic variant. Majority (50% to 100%) of tumours depict elevated serum chromogranin A, a feature which is concordant to tumour burden and metastasis [6,7].

Upon radiographic assessment, pancreatic neuroendocrine tumour appears as a spherical, solid, well circumscribed and hyper-vascular lesion. Cystic neoplasms may occur. Contrast enhanced computerized tomography (CT) exhibits minimal sensitivity while discerning miniature neoplasma < 2 centimetre magnitude. Magnetic resonance imaging (MRI) can be optimally employed, especially for exemplifying miniature neoplasms [6,7].

Gallium 68 dotatate positron emission tomography (PET) utilizes radiolabelled somatostatin analogue and appears beneficial, sensitive and specific for detecting well differentiated pancreatic neuroendocrine tumour (WDNET), majority of which manifest somatostatin receptors. Comprehensive surgical eradication is recommended for treating well differentiated neuroendocrine tumour. Optimal therapy induces symptomatic resolution of mass effect and hormonal secretions. Localized neoplasms or metastatic disease may be appropriately alleviated with surgical manoeuvers. Metastatic well differentiated neuroendocrine tumour is optimally managed with somatostatin analogue therapy or molecular agents comprised of tyrosine kinase inhibitor sunitinib or mTOR inhibitor everolimus [6,7]. Additionally, chemotherapy with capecitabine and temozolomide (CAPTEM), peptide receptor radionuclide therapy (PRRT) or liver directed therapy as ablation or hepatic artery embolization for eradicating hepatic metastasis may be optimally adopted [6,7]. Poorly differentiated neuroendocrine tumour is appropriately treated with platinum based chemotherapy. Tumour grading with World Health Organization(WHO) criterion concurs with prognostic outcomes, contingent to Ki67 labelling index and mitotic count [6,7]. Cogent immunohistochemistry concordant with prognostic outcomes enunciates expression of COX2, p27, CD99 or progesterone receptor(PR). Tumefaction with immune reactive CK19 exhibits aggressive biological behaviour [6,7].

References

1. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, et al. (2022) Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocr Pathol 33(1): 115-154.

2. Loosen SH, Kostev K, Eschrich J, Krieg S, Krieg A, et al. (2022) Clinical characteristics of 662 patients with pancreatic neuroendocrine tumors receiving antitumoral therapy. Medicine Baltimore 101(50): e32044.

3. Mariën L, Islam O, Van Mileghem L, Lybaert W, Peeters M, et al. (2022) Pathophysiology and Treatment of Pancreatic Neuroendocrine Neoplasms (PNENS): New Developments. Endotext Internet. South Dartmouth (MA).

4. Image 1 Courtesy: Pathology outlines

5. Image 2 Courtesy: Libre pathology

6. Li YL, Cheng ZX, Yu FH, Tian C, Huang-Ying T, et al. (2022) Advances in medical treatment for pancreatic neuroendocrine neoplasms. World J Gastroenterol 28(20): 2163-2175.

7. Sedhai S, Mohammed F, Sahtiya S, Sanaullah S, Pritwani P, et al. (2022) Pancreatic Neuroendocrine Tumor (PNET) Presenting as a Pseudocyst: A Case Report. Cureus 14(9): e29617.