Diagnosis and management of neuroendocrine tumours

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ABSTRACT

Neuroendocrine tumours (NETs) represent a heterogenous group of tumours, with diversity in their primary tumour sites, functional status (ie hormone secreting or non-functional) and degrees of aggressiveness (ranging from well-differentiated, grade 1 neuroendocrine tumours to poorly differentiated grade 3, neuroendocrine carcinomas). The most common sites are the lung, small bowel, pancreas and appendix. Clinical presentation is variable, ranging from incidental lesions detected on cross-sectional imaging, small bowel obstruction, carcinoid syndrome or other syndromic presentations (eg hypoglycaemia resulting from insulinoma) through to florid carcinoid heart disease. Diagnosis relies on biochemical markers, computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin-receptor based functional imaging. Treatment comprises surgery where curative resection is possible through to approaches where disease stabilisation is the key, involving somatostatin analogues, peptide receptor radionuclide therapy (PRRT), everolimus, sunitinib, liver-directed therapies and sometimes chemotherapy. Although local and systemic complications can occur, they are associated with reasonable 5- and 10-year survival rates, respectively.

Introduction

Neuroendocrine cells are found in almost every organ of the body and are also dispersed among other epithelial cells throughout the gastrointestinal and bronchopulmonary systems (the diffuse neuroendocrine system). The cells contain dense, core secretory granules, which synthesise, store and secrete serotonin and numerous other hormones/bioactive peptides with various functions in the gut, including nutrient sensing, gut secretions and motility, hormone release, and energy balance and appetite.

Neuroendocrine neoplasms (NENs) are rare tumours that derive from these neuroendocrine cells. They range in phenotype from poorly differentiated neuroendocrine carcinomas (NECs) to well-differentiated neuroendocrine tumours (NETs). NETs uniquely express cell-surface peptide hormone receptors, including somatostatin (SST) receptors (SSTRs). SST is a regulatory peptide hormone with a predominantly inhibitory function, inhibiting serotonin secretion and cell proliferation and/or growth through five SSTR subtypes (SSTR1–5). The presence of SSTRs on NETs can be exploited to facilitate imaging and treatment of these tumours with somatostatin analogues (SSAs) and peptide-receptor radionuclide therapy (PRRT).

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Epidemiology of NETs

Population-based studies from the UK and USA suggest that the incidence of NETs varies according to anatomical site: from 0.95 in appendix and 1.0 in pancreas (pancreatic NETs; panNETs) to 1.46 in small intestine (small intestinal NETs; SI-NETs) and 1.47 in lung per 100,000 people.[1] Thus, small bowel, pancreas [on the gastroenteropancreatic-NET (GEP-NET) spectrum] and lung (not discussed here) are the most common sites of disease. NETs are the second most-prevalent gastrointestinal tumour. Age-adjusted incidence has increased 3.7 fold over the past few decades, from 2.35 to 8.61 per 100,000 people, as a result of improved histological classification and recording, enhanced imaging and endoscopic techniques and possibly increased tumour development.[1] Overall 5-year survival varies between ~60% and

Key points

- Neuroendocrine tumours (NETs) most commonly arise in the small intestine, pancreas and lung
- NETs have frequently metastasised, with lymph node or hepatic metastases, by the time that patients present with symptoms
- SI-NETs are associated with symptoms of carcinoid syndrome (diarrhoea and flushing) in the presence of systemic spread, whereas panNETs can lead to a variety of functional syndromes
- Small bowel NETs can be associated with local complications (mesenteric ischaemia and bowel obstruction) or systemic complications (carcinoid heart disease)
- Patients are treated with surgery where cure is possible, although somatostatin analogues, peptide receptor radionuclide therapy, biological agents, liver-directed therapies and chemotherapy can also be used.

KEY WORDS: Neuroendocrine tumour, neuroendocrine carcinoma, carcinoid syndrome, somatostatin analogues, peptide receptor radionuclide therapy

DOI: 10.7861/clinmed.2023-0044

90%,but depends upon patient-specific factors (eg age, sex, and social deprivation) and tumour-specific factors (eg site, stage, morphology/grade and functionality/hormone secretion). Overall survival has improved significantly over the past decade.[2]

Small intestinal NETs

Small intestinal NETs (SI-NETs) classically arise in the distal ileum; 30–50% are multiple tumours with mesenteric lymph node metastases in >80%.[3] Patients can present with vague abdominal symptoms, leading to considerable diagnostic delay from first symptoms,[4] or with small bowel obstruction; alternatively SI-NETs are detected coincidentally on cross-sectional imaging, such as in patients presenting with a mesenteric mass (regional lymph node metastases). Patients frequently present with more advanced, metastatic disease (~50% with liver metastases, usually multiple/bilobar) because of symptoms of carcinoid syndrome (flushing and diarrhoea) relating to release of a variety of vasoactive peptides.[5] These peptides additionally cause mesenteric fibrosis, a desmoplastic reaction surrounding the tumour/mesenteric lymph nodes, causing colicky abdominal pain and potential bowel ischaemia, obstruction and even perforation. A further complication of NETs, occurring in ~20% of patients, is carcinoid heart disease (CHD), characterised by right-sided cardiac valvulopathy affecting the tricuspid and pulmonary valves,[6] with significant impact on prognosis.[7]

Pancreatic NETs

PanNETs account for 1–2% of all pancreatic cancers and can be divided into two groups, functional or non-functional, depending on the secretion of one or more hormones/peptides that lead to specific symptoms/clinical syndromes.[8] Approximately 60–90% of panNETs are non-functional, present late in the disease, often with distant metastases and, thus, patients might have shorter life expectancy than those with functional tumours. By contrast, functioning panNETs secrete active hormones, most commonly insulin or gastrin, leading to symptoms even when the tumour is small (Table 1). Significantly, panNETs can arise sporadically or as part of a cancer-predisposing syndrome, such as in multiple endocrine neoplasia Type 1 (MEN1), von Hippel-Lindau syndrome (VHL), tuberous sclerosis or neurofibromatosis. Functional panNETs arise occur more commonly in such familial syndromes compared with sporadic panNETs.

Diagnosis and staging

NETs can be classified according to their site of primary origin and the stage/disease extent (localised, locoregional spread or metastatic, eg to liver, lungs or skeleton). The diagnosis, accurate staging and grading of a NET rely on clinical presentation, blood-based biomarkers, cross-sectional (computed tomography (CT)/magnetic resonance imaging (MRI)) and functional hybrid imaging with positron emission tomography (PET)-CT and histological assessment of any biopsy/surgically resected specimens. Transthoracic echocardiography is used to assess patients for CHD.

Blood markers

Chromogranin A, a glycoprotein released by neuroendocrine cells, is the most widely used biomarker for determining tumour load with plasma/urine 5-hydroxyindolacetic acid (5-HIAA), a serotonin breakdown product, determining the functional/secretory activity of the tumour.[9] Additionally, both baseline and serial plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) provide information regarding the presence and severity of CHD.[10]

Cross-sectional imaging

CT scanning of the neck, chest, abdomen and pelvis is the mainstay of imaging for diagnosis, staging, surveillance and monitoring therapy response (Fig 1). However, bone metastases can be missed. MRI of the liver is advantageous for detecting liver metastases, and is recommended before liver surgery and for monitoring liver metastases.

Functional imaging

SSTR scintigraphy using single-photon emission (SPECT)-CT (octreotide scan) has been used historically, and might still be in some centres, but SSTR-based ^{68}Ga-PET–CT imaging (Fig 1) has emerged as the gold standard with greater diagnostic accuracy and lower radiation dose and frequently generally revealing additional sites of disease compared with CT/MRI (identifying an unknown primary tumour or other metastatic deposits).[11] This more accurate staging could change patient management. Demonstration of sufficient SSTR expression in the tumours renders the patient eligible for PRRT, should this be necessary. For higher grade tumours, metabolic imaging by flourine-18 fluorodeoxyglucose (^{18}FDG)-PET/CT imaging might be relevant.

ECHO/Cardiac CT/MRI

Approximately 20% of patients with carcinoid syndrome will have CHD, with the development of plaque-like, fibrous endocardial thickening of right-sided heart valves, relating to chronic exposure to excess circulating serotonin. Right-sided heart failure can develop, a complication that accounts for significant morbidity and mortality. Transthoracic echocardiography (TTE) is the key investigation for CHD diagnosis with monitoring using validated scores.[12,13] Cardiac CT and MRI (CCT/CMR) offer additional options, in cases with suboptimal TTE image acquisition or in pre-operative, valve replacement, assessment.

Histology

In addition to staging, NETs can be graded according to their morphological/histological appearance using the Ki67 proliferation index (Fig 2). NETS range from well-differentiated, slow-growing G1 and G2 tumours (G1/G2; Ki67 index <3% and 3–20%, respectively) to G3 tumours (Ki67 index >20%). G3 tumours can also be poorly differentiated and are described as NECs; with Ki67 >20%, NECs proliferate more rapidly, spread more quickly and have a much poorer prognosis.[14] These classification systems, based on Ki67 or differentiation, have validated prognostic value, independently predicting overall survival.

Treatment

Surgery

Surgery has a key role in management, with either curative or palliative intent (e.g., impending small bowel obstruction or for reducing secretory burden with functional NETS) (Fig 3). For those patients with metastatic/non-resectable NETs, a variety of therapeutic approaches are available.

Table 1. Functional syndromes associated with small intestine, pancreatic and bronchial neuroendocrine tumours

Tumour type	Cell type	Hormone secreted	Clinical features	Biochemical diagnosis	Prevalence in MEN-1
Pancreatic					
Insulinoma	β cells, islets	Insulin	Hypoglycaemia, Whipple's triad, clammy, sweating, weight gain	Either spontaneous or during 72-h fast: blood glucose ≤2.1 mmol/L; insulin levels >18 pmol/L; C-peptide levels ≥0.2 nmol/L; proinsulin levels ≥5 pmol/L; β-hydroxybutyrate levels ≤2.7 mmol/L No sulphonylurea metabolites in plasma and/or urine	10 %
VIPoma	D cells, islets	VIP	Werner–Morrison syndrome, watery diarrhoea	Plasma VIP levels >3 × ULN considered indicative of VIP-producing tumour	<1 %
Glucagonoma	α cells, islets	Glucagon	Diabetes mellitus, necrolytic migratory erythema, deep venous thrombosis, depression	Fasting plasma glucagon >500 pg/mL (normal 70–160 pg/mL) diagnostic for glucagonoma	<1 %
Somatostatinoma	D cells, islets	Somatostatin	Gallstones, Diabetes Mellitus, Steatorrhoea	Fasting plasma somatostatin concentration, >3 × ULN	5-10 %
Gastrinoma	G cells	Gastrin	Zollinger Ellison syndrome (gastroesophageal reflux, peptic ulcers, diarrhoea)	Serum gastrin above reference range	40 %
Non-functional	N/A	None	Symptoms related to mass effect	Normal gut hormones	20-55 %
Small intestine					
–	Enteroendocrine	Serotonin, kinins/ histamine	40 % of patients develop carcinoid syndrome (diarrhoea, flushing, abdominal pain, wheeze); fibrosis (mesenteric/ cardiac valves)	Plasma or urine 5-HIAA concentration; plasma chromogranin A	N/A
Bronchial					
–	–	Serotonin; histamine; ACTH	Majority are non-functional, 8 % carcinoid syndrome, atypical flushing; Cushing's syndrome	Usually normal gut hormones; elevated ACTH	2 %

5-HIAA = 5-hydroxyindoleacetic acid; ACTH = adrenocorticotropic hormone; MEN-1 = multiple endocrine neoplasia, type 1; ULN = upper limits of normal; VIP = vasoactive intestinal peptide.

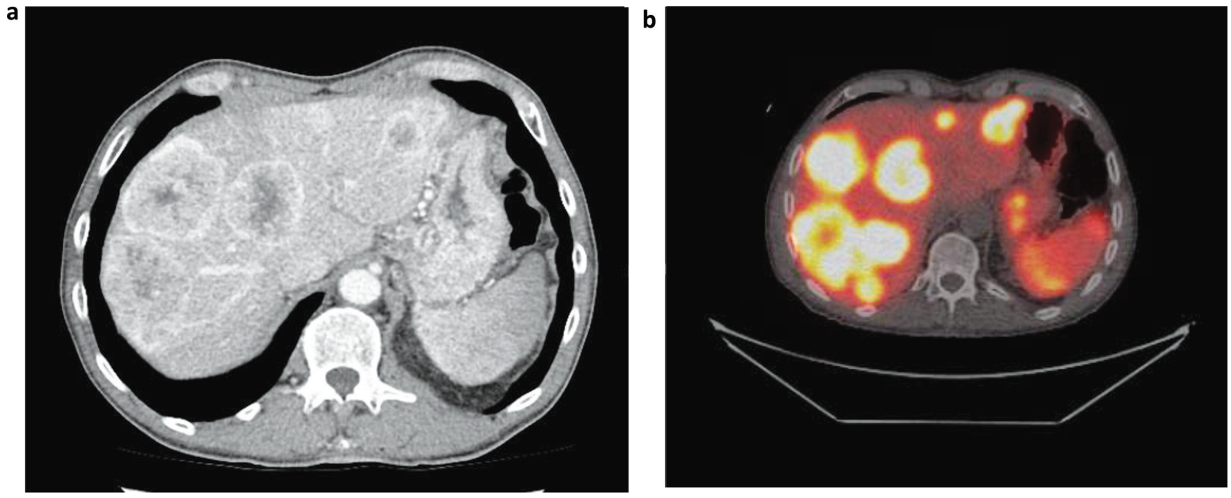

Fig 1. Cross-sectional (computed tomography (CT) scan, axial section, arterial phase) (a) and functional imaging (Ga^{68} positron emission tomography (PET)/CT scan, axial section) scan (b) showing multiple liver metastases in a patient with a metastatic neuroendocrine tumour.

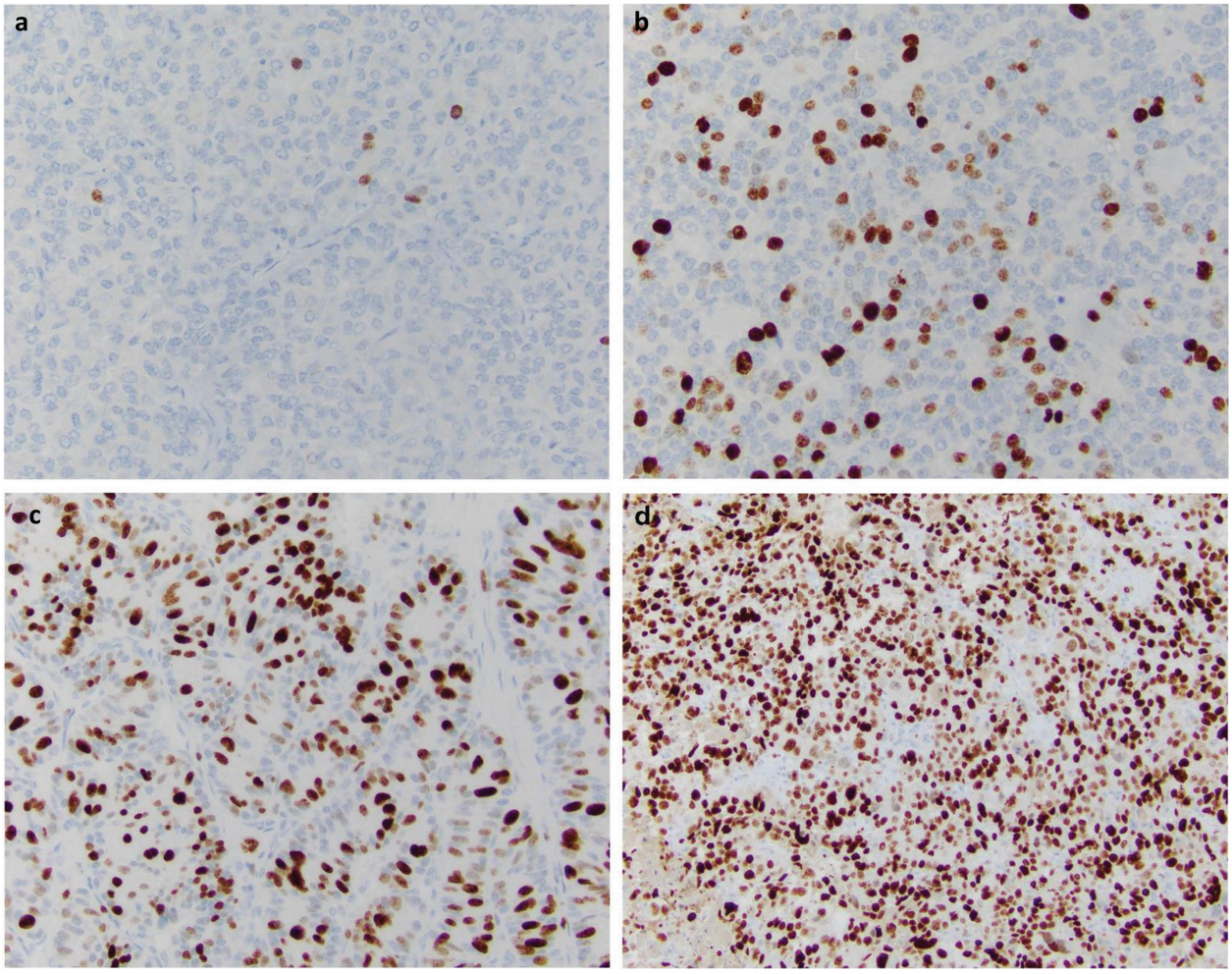

Fig 2. Molecular markers: Ki-67 staining of neuroendocrine neoplasms (neuroendocrine tumours (NETs)/neuroendocrine carcinomas (NECs)) from different sites: (a) grade 1 NET (ileum), (b) grade 2 NET (lung, atypical carcinoid), (c) grade 3 NET (pancreas) and (d) NEC (small cell lung cancer).

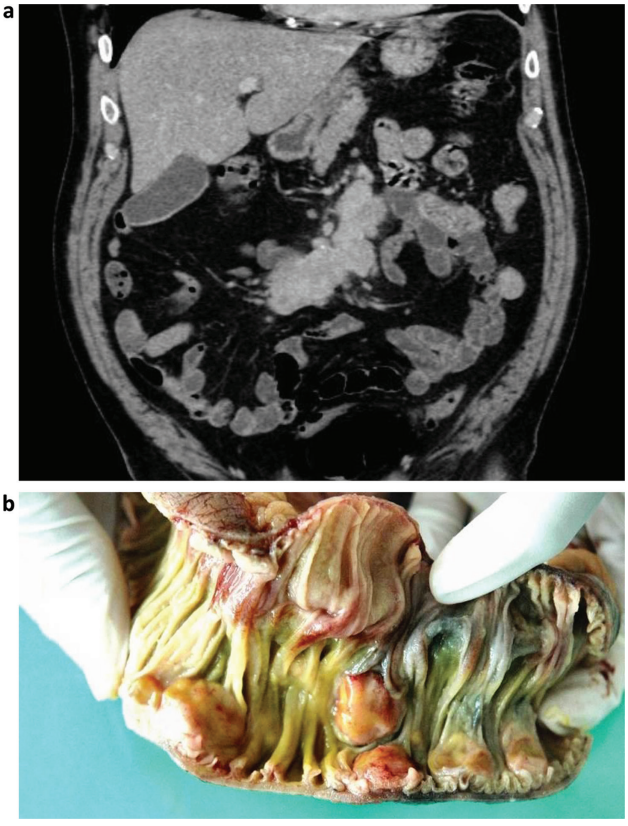

Fig 3. Large mesenteric mass associated with a small bowel neuroendocrine tumour (NET) (a) and a multifocal small bowel NET that was surgically resected (b).

Somatostatin analogues

SSAs represent the first-line therapy for NETs and were initially developed to reduce symptoms via reductions in hormone secretion in those with functional syndromes (eg carcinoid syndrome). Their additional antiproliferative potential was highlighted in two RCTs, PROMID and CLARINET.[15,16] PROMID, a placebo-controlled trial of 85 patients with low-grade, metastatic midgut NETs, demonstrated use of octreotide long-acting repeatable (LAR) versus placebo was associated with a greater median time to tumour progression (14.3 versus 6.0 months, respectively).[15] The CLARINET study, a placebo-controlled trial of 204 patients with locally advanced or metastatic non-functioning pancreatic and intestinal NETs, demonstrated that lanreotide versus placebo was associated with a greater median progression-free survival (PFS) (32.8 versus 18 months).[16] Although SSAs are effective at ameliorating symptoms of carcinoid syndrome, their adverse effects include nausea, abdominal cramps, diarrhoea, steatorrhoea, flatulence, hyperglycemia and cholestasis.

Peptide receptor radionuclide therapy

Lu^{177}-DOTATATE PRRT delivers targeted radiotherapy to sites of NET disease. For patients with SSTR-positive GEP-NETs, with progressive disease or refractory carcinoid syndrome, PRRT using ^{177}Lu-DOTATATE has been shown to offer disease control, improved quality of life and a survival benefit. It is administered as an intravenous infusion every 8–12 weeks. NETTER-1 was a phase III clinical trial, randomly assigning 229 patients with advanced midgut NETs to either ^{177}Lu-DOTATATE and octreotide LAR or high-dose octreotide LAR alone. Those that received ^{177}Lu-DOTATATE experienced a 54.4% increase in estimated PFS at 20 months versus control.[17]

Targeted therapies: everolimus and sunitinib

Everolimus is an option for treating well-differentiated (grade 1 or grade 2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease, based on data from the RADIANT trials.[18,19] Sunitinib is used to treat unresectable metastatic progressive panNETs.[20]

Cytotoxic chemotherapy

For those with NECs or NETs with a high Ki67 proliferation index, nd progression, cytotoxic chemotherapy can be considered to achieve a tumour response.

Liver-directed therapies

Considering the severity of symptoms associated with tumour burden, reduction of liver tumour burden can reduce symptoms that are either mass related and/or related to hormonal hypersecretion. Liver metastases can be resected or treated with a variety of interventional radiology techniques (bland embolisation, radioembolisation/selective internal radiation therapy (SIRT), radiofrequency ablation (RFA), microwave/cryoablation, and irreversible electroporation (IRE)).

Sequencing of therapy

There is currently no consensus on the optimal sequencing of therapies for treating NETs.

Conclusion

NETs require multidisciplinary expertise considering the wide array of clinical presentations and management options. Treatments aim to manage symptoms resulting from hormonal hypersecretion and local and systemic complications, and have an antiproliferative effect. Prognosis is generally good, with encouraging 5- and 10-year survival rates. ■

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