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PARANEOPLASTIC SYNDROMES RELATED TO NEUROENDORINE TUMOURS

Gregory Kaltsas
M.D., FRCP, Professor, Department of Pathophysiology, Sector of Endocrinology, National and Kapodistrian University of Athens, Greece, Medical School, Mikras Asias 75, 11527 Goudi, gkaltsas@endo.gr

Georgios K.Dimitriadis

Ioannis I. Androulakis
Endocrine unit, Department of Pathophysiology, Medical School, University of Athens, Athens, Greece

Ashley Grossman, BA BSc MD FRCP FMedSci
Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, UK

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ABSTRACT

Low or high grade malignant neoplasms present syndromes secondary to symptoms related to local mass effects to surrounding structures or through the development of metastases. A significant number of neoplasms, irrespective of their endocrine differentiation, can present with clinical syndromes produced from the secretion of bioactive substances from tumoural cells, although this is more prevalent in neuroendocrine tumours. Occasionally syndromes related to the immune cross-reactivity of tumoural antigens with the normal tissues may also develop. These syndromes are named endocrine paraneoplastic when the specific secretory components (hormones, peptides or cytokines) are unrelated to the anticipated tissue or organ of origin. Endocrine paraneoplastic syndromes can precede, occur concomitantly or present at a later stage of tumour development and may complicate the patient's clinical course, response to treatment, and impact overall prognosis. Their detection can facilitate the diagnosis of the underlying neoplasia, monitor response to treatment, detect early recurrences and correlate with prognosis. Although when associated with tumours of low malignant potential they usually do not affect long-term outcome, in cases of highly malignant tumours, endocrine paraneoplastic syndromes are usually associated with poorer survival outcomes. Currently, no specific underlying pathogenic mechanism has been identified although a number of plausible hypotheses have been put forward. However, advances in the localization and treatment of these syndromes have evolved and aim at early identification particularly as the number of these syndromes is expected to rise. The development of well-designed prospective multicentre trials remains a priority in the field in order to fully characterise these syndromes and provide evidence-based diagnostic and therapeutic protocols. For extended coverage of this and related topics, please see our FREE on-line web- text www.endotext.org.

INTRODUCTION

Neuroendocrine tumours (NETs) are considered to be relatively rare, but their prevalence is increasing in recent extended databases (1). Traditionally, histology, immunohistochemistry and electron microscopy have all been used as means to denote the neuroendocrine (NE) origin of these tumours. However, currently their diagnosis is depended on the demonstration of immunohistochemical markers of NE differentiation such as chromogranin A (CgA) and synaptophysin. Based on the presence of these markers the distribution of tumours regarded as NETs is shown in Table 1. Although some of these tumours may exert mostly a benign behavior (pituitary and parathyroid adenomas and the majority of pheochromocytomas) the remaining are considered to be malignant. However, in this latter group the malignant potential of the different type of tumours varies significantly ranging from slowly growing tumours with minimal metastatic potential to very aggressive and rapidly metastasizing tumours. Most NETs are well differentiated and may exhibit prolonged survival besides the presence of extensive disease. Traditionally tumours derived from NE cells of the gastrointestinal (GI) system have been named “carcinoids” reflecting their less malignant behavior compared to other type of cancers (2). The recent classifications of the WHO and the European Neuroendocrine Tumour Society (ENETS) for GI NETs have distinguished them according to their malignant potential based on the mitotic index and the estimation of the Ki-67 labeling index (LI) (3) (Table 2). In addition, the term ‘carcinoid’ has been replaced with that of ‘neuroendocrine tumour and carcinoma’ reflecting their true malignant potential. Although the introduction of the Ki-67 LI has been fully evaluated in NETs originating from the GI-system, it appears that may be also useful in other types of NETs such as chromaffin cell tumours, medullary thyroid carcinoma (MTC) and pituitary tumours (4-6). NETs from all of these histopathological entities have the ability to synthesize and secrete biologically-active and inactive products (2;7).

Table 1Tumours regarded as NETs based of the immunohistochemical expression of the markers of NE-differentiation chromogranin A (CgA)

CgA positive neuroendocrine tumours by immunohistochemistry	
Anterior pituitary tumours	ECL-oma
• NFPA	Small/large cell lung carcinoma
• PRL secreting adenoma • GH secreting adenoma	Gastrinoma
• ACTH secreting adenoma	Insulinoma
• TSH secreting adenoma	VIP-oma

• FSH/LH secreting adenomas	Glucagonoma
Parathyroid tumours	Somatostatinoma
Medullary thyroid carcinoma	Phaeochromocytoma
Carcinoids (foregut, midgut, hindgut)	Paraganglioma
Neuroendocrine gastroenteropancreatic (GEP) tumours	Neuroblastoma, ganglioneuroma
Non-functioning pancreatic neuroendocrine tumours	Merkel cell tumour
Thymoma	
CgA: Chromogranin A, NET: Neuroendocrine tumours, NFPA: Non-functioning pituitary adenoma, ECL: entero-chromaffin like cells, PRL: Prolactin, CgB: Chromogranin B, GH: Growth hormone, ACTH: adrenocorticotropin hormone, TSH: thyreotropin hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone,*: the term gastrointestinal neuroendocrine tumours includes this entity considering the anatomic origin of the different tumours	

Table 2 Classification of GI neuroendocrine tumours: traditional versus current

Mitotic count/10HPF*	Ki67 index (%)	Traditional classification	WHO/ENETS classification
< 2	≤ 2	Carcinoid, islet cell neuroendocrine carcinoma	Neuroendocrine tumour grade 1
2-20	3-20	Carcinoid, atypical carcinoid, ** islet cell neuroendocrine carcinoma	Neuroendocrine tumour grade 2
>20	> 20	Small cell carcinoma Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3, small cell Neuroendocrine carcinoma grade 3, large cell

HPF — high-power field; ENETS — European Neuroendocrine Tumour Society; *HPF = 2 mm2; at least 40 fields (at X magnification) in areas of highest mitotic density. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition); **MIB1 antibody; percentage of 2,000 tumour cells in areas of highest nuclear labeling. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition); ***The term atypical carcinoid only applies to immediate-grade neuroendocrine tumour of the lung (3)

The secretory products of NETs, peptides and amines, are characteristic of the tissue of origin and some can be biologically active causing distinct clinical syndromes (Table 3). These tumours can occur either sporadically or in the context of Multiple Endocrine Neoplasia (MEN) syndromes. Secretory tumours are denoted “functioning” in order to be distinguished from tumours originating from NE cells which do not produce any substances associated with recognized clinical syndromes or produce biologically inactive substances that do not have any clinical consequences (2;8). The latter tumours are called “non-functioning” and cause symptoms, along with functioning tumours, due to mass effects and compression of surrounding vital structures (2;9).

Table 3

SITE	Tumour	Cases/106	Peptide/amines	Clinical feature
Foregut	Bronchi, thymus, stomach, first part of duodenum, pancreas	2-5	5-HTP, histamine, ACTH, CRH, GH, gastrin, 5-HIAA	Pulmonary obstruction, atypical flush, hormone syndrome
Midgut	Second part of duodenum, jejunum, ileum, right colon	4-10	5-HT, tachykinins, prostaglandins, bradykinins and others (70%), 5-HIAA (75%)	Bowel obstruction, typical pink/red flush, wheeze/ diarrhea
Hindgut	Insulinoma	1-2	Insulin, proinsulin	Whipple's triad
	Gastrinoma	1-1,5	Gastrin	Zollinger-Ellison syndrome
	VIPoma	0.1	VIP	Watery diarrhea, hypokalemia
	Glucagonoma	0.01-0.1	Glucagon	DM, cahexia

	Somatostatinoma	<0.1	SS	Gallstones, DM, steatorrhea
	GRFoma	<0.1	GRF	Acromegaly
	ACTHoma	<0.1	ACTH	Cushing's Syndrome

GI: gastrointestinal system, ACTH; adrenocorticotropin, CRH: corticotrophin releasing hormone, GH: growth hormone, 5-HIAA: 5-hydroxy-indoloacetic acid, HT: hydroxytryptamin, VIP: vasointestinal peptide, SS: somatostatin, GRH: growth hormone releasing hormone, DM: Diabetes Mellitus

Patients with neoplastic tumours may occasionally present with symptoms that cannot be explained by the presence of the neoplastic lesion in a specific anatomic site (10). The term “paraneoplastic syndromes” (PNSs) is used to denote a spectrum of symptoms secondary to the production of hormones, growth factors, cytokines and/or others substances by the tumour cells not designated to release these specific compounds and can originate from either endocrine or non-endocrine neoplasms (8;11). The occurrence of PNS is influenced by the histology of the underlying neoplasm, and while such behaviour can often be explained in tumours of endocrine origin, it is not as yet fully understood in cases of non-endocrine neoplasms. In order a spectrum of symptoms to be qualified as PNS several clinical, biochemical and histopathological criteria have to be fulfilled (Table 4).

Table 4 Criteria for defining a PNS

• Clinical Presence of a distinct clinical syndrome attributed to a secretory product
Remission or improvement of the syndrome following treatment and/or reappearance following recurrence
• Biochemical Abnormally regulated elevated secretory product and/or significant gradient between the venous effluent of the tumour and the arterial level of the same product
• Histopathological Presence of bio/immuno-reactive and relevant mRNA of the secretory product in tumour tissue

Synthetic and secretory ability of the product by tumour cells *in vitro*

The vast majority of these syndromes are the secretory products of NE-cells, mainly peptide hormones and amines (Table 3) [2,4]. Occasionally, autoantibodies that cross-react with other tissues are produced leading to a variety of syndromes mainly involving the neurological system (Table 5) (8;12;13). The clinical manifestations of these ectopic hormonal secretion syndromes may be clinically indistinguishable to those encountered when the neoplastic lesion is found in the expected site of origin (eutopic hormonal secretion), thus causing diagnostic dilemmas (10;14). (Table 1). NETs are the type of tumours that are expected to exhibit the highest prevalence of PNSs due to their inherent synthetic and secretory capacity (15).

Table 5 Neurological, dermatological paraneoplastic syndromes and responsible autoantibodies related to NETs

Neurological PNS	Lambert-Eaton myasthenic syndrome(LEMS)	Cerebellar degeneration	Limbic encephalitis	Visceral plexopathy	Cancer-associated retinopathy	Autonomic dysfunction
Responsible Auto-Ab	Anti-voltage-gated calcium channels (P/Q type)	-	Anti-Hu, anti-Ma2	type 1 antineuronal nuclear antibodies	Anti-23 kd CAR antigen	-
NET	SCLC, carcinoid	SCLC	SCLC, carcinoid	SCLC	SCLC	SCLC, carcinoid
Dermatological PNS	Scleroderma-like	Palmar fasciitis	Flushing-Rosacea	Dermatomyositis	TEN-like syndrome	Pellagra
NET	SCLC, carcinoid	SCLC	SCLC, carcinoid	SCLC	SCLC	SCLC, carcinoid

PNS: Paraneoplasmatic Syndromes, NET: Neuroendocrine Tumours, SCLC: Small cell lung carcinoma, TEN-like: Toxic Epidermal Necrolysis-like syndrome

DIAGNOSTIC METHODS

PNS can develop during different phases of the evolution of the neoplastic process, with an estimated prevalence of approximately 8% considering all malignant neoplasms (16). In some cases, PNS can present before the diagnosis of the underlying malignancy and help making the diagnosis at an early disease stage (17). Furthermore, the presence of PNS and related aetiological factor can be used to monitor response to treatment and/or detect early recurrence of the tumour. Effective and prompt diagnosis and treatment of the PNS may

substantially improve overall clinical outcomes. However, in the presence of highly aggressive tumours or extensive disease burden, management of these syndromes may be difficult (14). As currently available therapies for a number of neoplasms evolve and highly specific diagnostic modalities become widely used, patients with tumours will live longer, and thus the prevalence of PNS will likely also increase (18). Herein, only endocrine PNS related to NETS will be considered, excluding those related to different pathophysiological processes and/or exhibiting manifestations in other systems.

Following the diagnosis of a NET several clinically important issues should be addressed regarding the extent of the disease (staging), tumour biology and the occurrence of the tumour either as a sporadic tumour or in the context of inherited syndromes, mainly MEN (9). Over the last decades, two important advances, scintigraphy with 111In-labelled octreotide (somatostatin receptor scintigraphy, SRS), and serum estimation of the universal NET marker CgA, have contributed substantially to this field (Figure 1, 2). In addition, scintigraphy with 123-I-meta-iodo-benzylguanidine (MIBG) has a high sensitivity and specificity in identifying tumours originating from chromaffin cells and may be of value in SRS negative lesions (Figure 3). The reported overall sensitivity of SRS for well-differentiated (grade 1 and 2) GI-NETs is >80%. The sensitivity of SRS is lower in tumours with a diameter <1cm, due to insufficient tumour-to-background uptake ratios of radioactivity, and is also low in NETs with a high Ki-67 index or neuroendocrine carcinomas (NECs), reflecting dedifferentiation and loss of sstr expression (19). SRS has recently been surpassed by the introduction of newer agents such as 68Gallium-DOTATE (DOTANOC) PET/CT that exerts a higher sensitivity in the identification and localization of NETs (20). Furthermore, some advocate that the combination of 68-Gallium with 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) may be of relevant clinical significance as it can identify less differentiated tumours that exert a more aggressive course (15). ^{123}I-MIBG scintigraphy has lower sensitivity than SRS for GI-NETs (50%) and pancreatic NETs (<10%) (21). Fluorine-18-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET/CT showed the highest sensitivity (98%) and ^{11}C-5-hydroxy-L-tryptophan (11C-5-HTP) PET for the detection of GI-NETs (22). ^{11}C-5-HTP is a radiolabelled precursor in the serotonin synthesis: ^{11}C-5-HTP PET showed a 96% sensitivity for the detection of pNETs (23). Cholecystokinin$_2$ (CCK2) receptor expression has been demonstrated in NETs with ^{111}In-DOTA-CCK, ^{99}mTc-demogastrin and ^{111}In-DOTAMG11. Another radiopeptide used for targeting the GLP1R is (Lys(40)(Ahx-HYNIC-^{99m}Tc/EDDA)NH2)–exendin-4, GLP1R imaging using this compound has been studied in MTCs (24).

The wide application of these modalities has contributed immensely to the identification and characterization of PNSs derived from NETs. In addition, a number of autoantibodies have been shown to be of diagnostic significance in neurological PNSs (Table 5).). Besides traditional biomarkers developed for the detection of endocrine malignancy, there is currently considerable interest in areas such as blood transcript
analysis, circulating tumour cells, mRNA transcripts (NetTest) and miRNA measurement, although there are yet significant limitations before application into general clinical practice is likely (25).

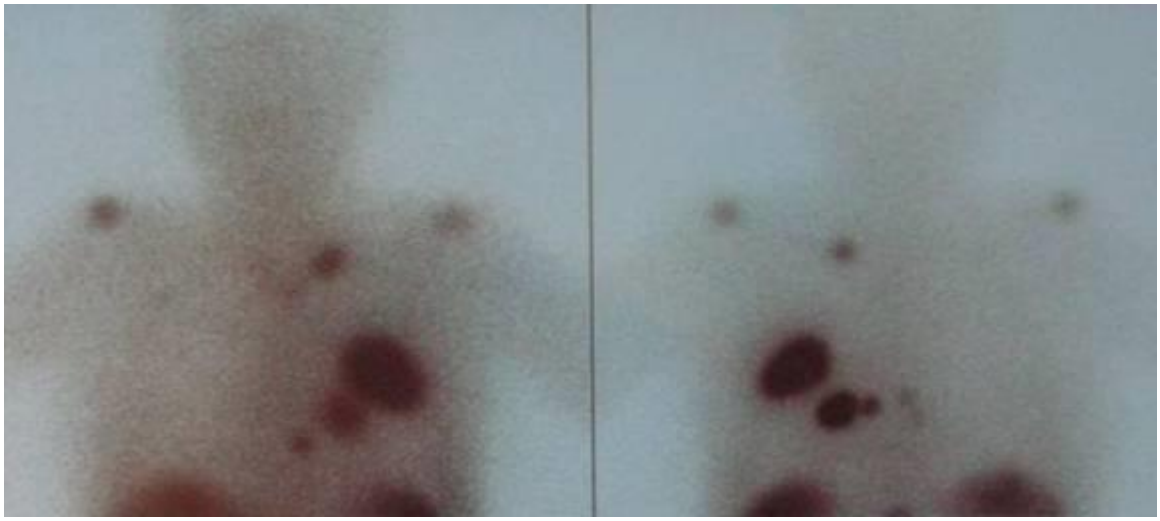

Figure 1

SRS (scintigraphy with 111In-octreotide). Anterior view in a patient with Cushing's syndrome due to ectopic ACTH secretion revealing increased areas of uptake in the left upper lung, both clavicles and sternum, which proved to be metastases from an atypical bronchial carcinoid tumour.

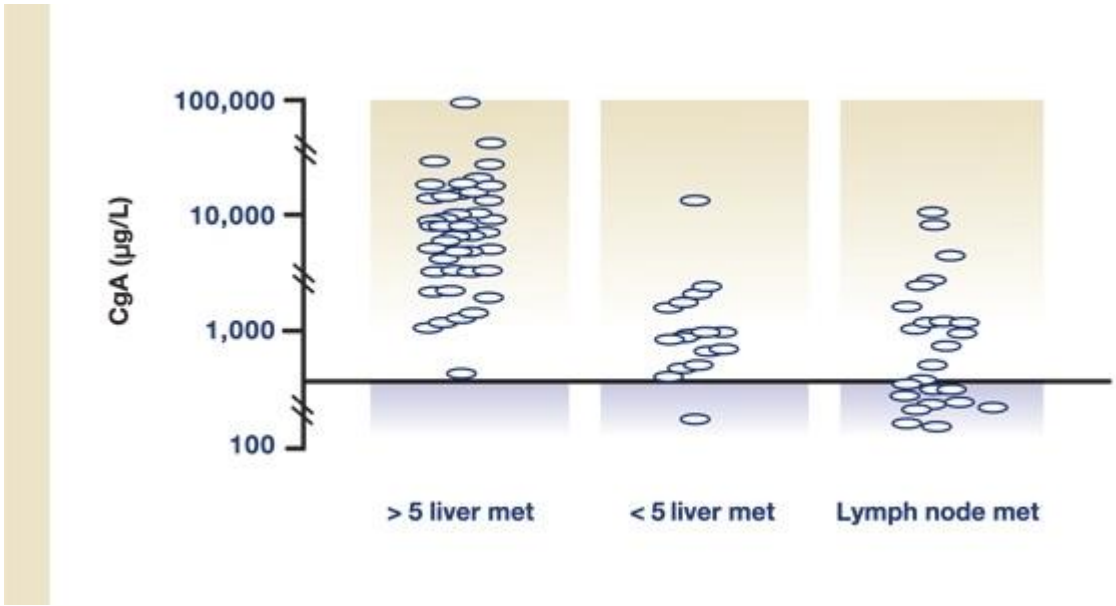

Figure 2 Chromogranin A measurement as an indicator of tumour load in patients with NETs

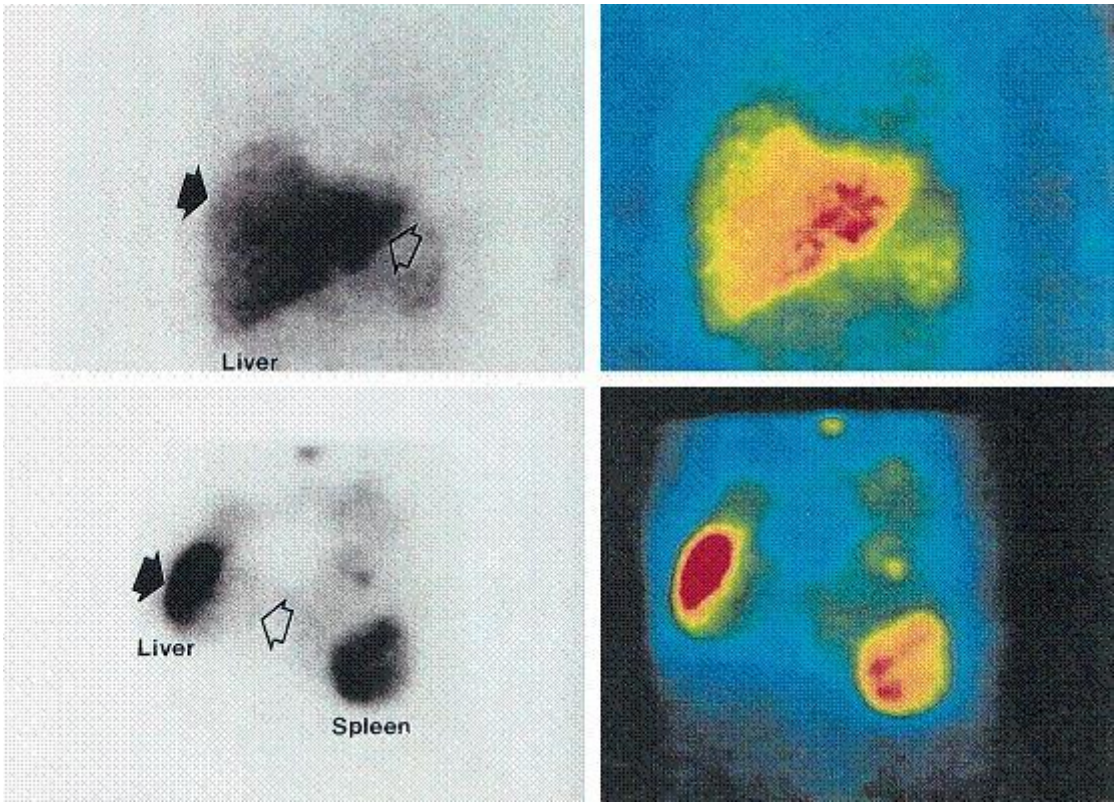

Figure 3 Qualitative difference in the pattern of uptake with [123I]MIBG (upper part of figure), and Octreoscan (lower part of figure) scintigraphy in the same patient with hepatic metastases from an ileal carcinoid.

PATHOGENESIS

The exact pathogenesis that leads to the development of PNSs is not known. Neoplastic transformation is linked to alterations of oncogenes, tumour suppressor genes and apoptotic mechanisms that control cell growth (12;13). All human cells carry the same genetic information of which only part is expressed through their life span. However, under certain conditions specific alterations of gene function may activate genes that regulate hormonal synthesis, particularly in the context of an underlying neoplastic process, leading to the development of neuroendocrine PNS (265). Inappropriate gene expression heralds the unscheduled appearance of a gene product at an unusual time of life or in an atypical cell, tissue or organ leading to a PNS, as encountered in many different animal species (17). The same mechanisms may also operate to initiate PNSs, i.e. by activating hormone production, changing the activity of genes that regulate the expression of genes involved in hormonal synthesis, or by antibody formation (12;15). Ectopically-produced substances are mainly peptides or glycoproteins and PNSs are produced by the direct secretion of these substances from the tumour arising from tissue other than the endocrine gland or tissue that normally produces them (12) PNSs may also develop secondary to antibody formation induced by the expression of immunoaccessible antigens usually expressed in neuronal tissue (15) (Table 5). However, the precise mechanism that initiates ectopic hormonal synthesis and release during the neoplastic transformation at a specific time point stills remains to be defined (14).

Humoral paraneoplastic syndromes in NETs (Table 3)

Hypercalcaemia

Humoral hypercalcemia is one of the commonest PNSs. Approximately 5% of patients with malignant tumours develop hypercalcaemia, but its prevalence has not precisely been estimated in patients with NETs (12;20). Almost all cases of NET-related hypercalcaemia are associated with hypophosphataemia suggesting a parathyroid, PTH-like effect. Parathyroid hormone-related protein (PTHrP) is now considered to be the main mediator of humoral hypercalcaemia of malignancy in patients with NETs (13,15). It has effects upon tissues other than bone, including the skin, anterior pituitary and mammary gland, and causes more widespread symptoms than elevated PTH although there is some overlap (27). Hypomethylation of the promoter has been implicated as a mechanism of its aberrant gene expression (28).

The first case of a PTHrP-producing malignant NET was described in a pancreatic islet cell tumour (pNET) with more than 30 of cases been documented (28-30). The majority of these tumours are well differentiated carcinomas but in contrast to other PTHrP-secreting malignancies have a much better outcome (20;31). However, a recent single centre study identified this to be a relatively rare event (32). Interestingly, a case of a brown tumour in a patient with long-standing PTHrP related hypercalcemia has been described confirming the relevant biological homology of this peptide to the native hormone (20). Benign phaeochromocytomas can also secrete PTHrP and cause hypercalcaemia (33). Very few cases of ectopic PTH secretion from NETs have been documented mainly from small cell lung carcinomas (SCLC), and MTC (34-36). In a recent literature review, 32 patients with tumours originating from the head and neck (7), thorax (8), GI-pelvis (11) and gynaecological (5) neoplasms, including a number of endocrine and NETs, were reported causing hypercalcaemia secondary to PTH secretion (37).

Although successful treatment of the underlying neoplasm usually suffices to control the clinical symptoms and systemic sequela of hypercalcemia, in cases of severe disease medical treatment of hypercalcemia is also required (38). In such cases, the calcimimetic cinacalcet has been shown to be efficacious in a case of a parathyroid carcinoma, whereas multiple anti-tumours modalities may be required to control cases of refractory hypercalcemia in inoperable patients (30;39).

Ectopic vasopressin (ADH) & atrial natriuretic peptide (ANP) secretion

Although vasopressin is produced within the hypothalamus and stored in nerve terminals of the posterior pituitary, additional processing can also occur in SCLC cells and other neoplasms that can also synthesize and secrete oxytocin (40;41). A syndrome of renal sodium loss and hyponatremia resulting from inappropriate ADH secretion (SIADH) was first described in the early 1950s (42). Although vasopressin levels are increased in up to 50% of patients with SCLCs, only 15% develop the syndrome (43). Similarly, elevated plasma oxytocin levels are found in up to 20% of patients with SCLCs (43;44). Atrial natriuretic peptide (ANP) is synthesized from the cardiac atria and can initiate natriuresis and hypotension when ectopically produced by NETs (45;46). In contrast to the majority of chronic causes of hyponatremia that may develop gradually and be relatively asymptomatic, hyponatremia secondary to ectopic hormonal production can develop abruptly and be

associated with severe symptoms (47). In SCLC, SIADH has been associated with a higher propensity for central nervous system metastases, poor response to chemotherapy and advanced stage of cancer (48). There appears to be no clinical and/or biochemical features distinguishing the origin of the tumour although most severe symptoms are encountered in patients with highly aggressive tumours (49); hyponatraemia grade at short-term follow-up was also predictive for long-term survival (50). The diagnosis of SIADH secretion is made by demonstrating a urinary osmolality that exceeds 100mOsm/kg of water in the presence of low effective plasma osmolality in a euvolemic individual. Treating the underlying neoplasm is the best means of correcting the hyponatraemia (51). In the absence of symptoms, gradual correction of the hyponatremia is appropriate and involves adequate solute intake and fluid restriction (51;52). In the presence of symptoms increasing serum sodium by 0.5-1 mmol/L/hour for a total of 8 mmol/L during the first day is required to render the patient asymptomatic; this can be enhanced by promoting free-water excretion with furosemide (51). Alternatively, the management of SIADH may be enhanced by the recent introduction of the vasopressin antagonists “vaptans”, that can raise Na+ levels up to 5 mEq/L/day (52;53). It has recently been shown that prompt endocrine input improved time for correction of hyponatraemia and shortened length of hospitalisation, and the widespread provision of endocrine input should be considered (54-56).

Cushing's syndrome (CS)

Cushing’s syndrome (CS) as a PNS accounts for 10%-20% of the total cases of CS and develops secondary to tumoural adrenocorticotropin (ACTH), and less often to corticotrophin-releasing hormone (CRH) production (57;58). NETs associated with CS are mainly derived from the lung, thymus, pancreas, thyroid (MTC), chromaffin cell tumours (phaeochromocytomas, paragangliomas, neuroblastomas), and rarely from the ovary or prostate (59). Bronchial carcinoids (typical and atypical) account for 36%-46% of these cases, whereas the highly malignant SCLC accounts for 8%-20% of clinically-apparent cases (58;60). However, up to 30% of SCLCs hypersecrete ACTH that may be bio-inactive following incomplete processing and thus not capable of inducing a clinical syndrome (58;60). The ectopic ACTH syndrome is caused by abnormal expression of the POMC gene product in response to ectopic activation of the pituitary-specific promoter of this gene. Using bisulphite sequencing and hypomethylation in five thymic carcinoid tumours resected from patients with ectopic ACTH syndrome, its presence correlated with POMC over-expression and the ectopic ACTH syndrome (61). Methylation near the response element for the tissue-specific POMC activator PTX1 diminishes POMC expression, implying that the methylation and expression patterns are likely to be set early or prior to neoplastic transformation and that targeted *de novo* methylation might be a potential therapeutic strategy (62). The CS produced by bronchial carcinoids clinically and biochemically resembles pituitary-dependent CS (Cushing’s disease, CD); in contrast, patients with CS secondary to SCLCs do not typically exhibit the classical manifestations of prolonged and sustained hypercortisolaemia, but rather those of the underlying malignancy (15;60;63;64). Approximately 8-20% of PNS-CS is related to SCLC, although the secretory potential of ectopically produced ACTH of these tumours is much higher than that encountered in NETs (59, 13, 14). The impact of PN-CS has been evaluated in 383 patients with SCLC, 23 of whom had PN-CS, 56 other PNS (OtherPNS), and 304 had no PNS (NoPNS). (65). After comparison of the three groups, PN-

CS patients had more extensive disease, greater weight loss (≥10%) and a reduced objective response to first-line treatment) 47.6% versus 74.1% versus 71.1%) and poorer sensitivity to first-line treatment (19% versus 38.9% versus 48.6%) respectively. On relapse, the PN-CS group had no objective response to second-line treatment versus 25% and 42.8% in OtherPNS and NoPNS groups respectively (65). The median survival of PN-CS patients was 6.6 months versus 9.2 months for otherPNS and 13.1 months for noPNS patients. It was concluded that PN-CS is a prognostic factor of early demise (hazard ratio, 2.31) (65).

The incidence of CS secondary to MTCs is less than 1%, with approximately 100 cases reported, whereas CS due to chromaffin cell tumours is even rarer with less than 30 reported cases (66;67). Rarely CS may result from CRH production from SCLCs, MTCs, carcinoids, pNETs, and chromaffin cell tumours accounting for approximately 5.2% of all cases of ectopic ACTH related CS (20; 68-71). In such cases, patients have high CRH levels in plasma and tumour tissue whereas plasma ACTH levels are also increased; CS due to CRH production does not have a distinctive presentation and endocrine testing may represent an interplay between ectopic and eutopic production (20;69-71).

Treatment relies on successful control of the underlying malignancy. Occasionally hypercortisolism may be extremely severe and difficult to control with adrenolytic medication, necessitating bilateral adrenalectomy. When rapid correction of the hypercortisolemia is required intravenous etomidate can be used; long acting somatostatin analogs including the multipotent somatostatin receptor inhibitor pasireotide can be considered in specific cases (72). Mifepristone, an antagonist of glucocorticoid receptors, has also been used to control excessive hypercortisolaemia secondary to disseminated NETs (73). However, as its effects can only be monitored clinically and is associated with hypertension and hypokalemia, its use is limited (73).

Acromegaly

Acromegaly secondary to non-pituitary tumours is rare and accounts for less than 1% of cases of acromegaly mostly related to growth hormone-releasing hormone (GHRH)-hypersecretion and rarely to growth hormone itself (GH) (74). NETs most commonly associated with GHRH hypersecretion are carcinoids, pNETs, SCLCs and phaeochromocytomas (75-77). Clinical presentation is not different to that of pituitary origin but endocrine testing cannot reliably distinguish these tumours from pituitary adenomas (75;78). In contrast to the presence of pituitary adenomas in patients with classical acromegaly, the pituitary pathology in patients with ectopic GHRH secretion and acromegaly is that of uniform pituitary enlargement due to GH-cell hyperplasia (75;79). Only a few patients with acromegaly due to GHRH-producing pNETs from patients with the MEN-1 syndrome have been described (75;80). A further two cases of ectopic GH secretion, one from a pNET, have also been described (81;82). Treatment is that of the underlying tumour and relates to the extent of the disease. In NETs arising from the gastrointestinal system, long acting somatostatin analogs can also be useful for the treatment of the tumour and the PNS (83).

Hypoglycaemia

Tumours not derived from pancreatic islets may produce recurrent fasting hypoglycaemia, a condition called non-islet cell tumour hypoglycaemia (NICTH) (84). This condition is mainly secondary to the hypersecretion of insulin growth factor 2 (IGF2) precursor that is not cleaved producing increased amounts of “big-IGF2″. This molecule has a molecular mass of 10-17 kDa, that is substantially bigger to the 7.5 kDa of mature IGF2. This structure has substantially reduced affinity to its cognate binding protein (85;86), leading to increased free levels that exerts its effect to insulin and IGF receptors. As a result, serum insulin is low and serum GH levels are suppressed contributing further to hypoglycaemia; IGF1 levels are usually also low (84;87). Although “big-IGF2” is mostly secreted by tumours of mesenchymal and epithelial origin, rare cases of NETs have also been described (85;88). The possibility of hypoglycaemia due to insulin secretion from non islet-cell tumours is controversial and a few cases of carcinoid tumours metastatic to the liver have been described (88-90). Following these reports further cases of an insulin-secreting NET of the cervix and two paragangliomas have been described (84;91). A rare case of a large cell lung carcinoma with recurrent hypoglycaemia, low insulin and big IGF2 levels, and increased IGF1 levels, has also been described (92). In a recent review, 32 cases of IGF-2 secreting tumours with hypoglycaemia that underwent radical surgery were identified; in 19 patients, hypoglycaemia was reversed and there was no subsequent recurrence. The remaining 13 patients experienced tumour recurrence or metastasis an average of 43 months after initial tumour resection (93). Treatment relates to that of the underlying neoplasm, stage and grade of the disease. Patients with NICTH may undergo complete remission following surgical removal of the tumour; even partial removal often may reduce or abolish the hypoglycaemia (94). Both human GH and prednisolone can induce a substantial effect (95;96); although long acting somatostatin analogs can also be used this should be done with caution as they can inhibit the secretion of counter-regulatory to hypoglycaemia hormones (83). Although mTOR pathway blockade may represent a possible target regarding the management of malignant insulinoma-induced NICTH, an interesting case of an adrenocortical carcinoma secreting IGF-2 not responding to everolimus was recently reported (97). It appears that either IGF-2 does not cause hypoglycaemia by activation of the insulin receptor, which is improbable, or that the mode of action of everolimus in this situation was not downstream of the insulin receptor. It is possible that the IGF1-R and insulin receptor A or B may form receptor hybrids when co-expressed on the same cell (97).

Ectopic secretion of other peptidic (including pituitary) hormones

Although extremely rare, a few cases of ectopic luteinizing hormone (LH) production from pNETs have been described (98;99). No definite case of ectopic TSH has clearly been described (15;100), whereas ectopic prolactin production has been reported in association with SCLCs (9;20). Tumour-associated β-human chorionic gonadotrophin (β-hCG) production has been demonstrated in SCLCs and pNETs clinically associated with gynaecomastia in men, menstrual irregularity and virilisation in women and precocious puberty in children (20). Ectopic renin secretion is extremely rare and has been described in a SCLC, paraganglioma, and a carcinoid tumour accompanied by hypertension and hypokalemia; an increased ratio of pro-renin to renin is found due to inefficient processing of renin by the tumours (101;102). A few cases of ectopic production of vasoactive instestinal polypeptide (VIP) causing watery diarrhea arising from a SCLC, MTC, and a phaeochromocytoma have been described (103). Several cases of phaeochromocytomas presenting with flushing, hypotension or normal pressure plus excessive catecholamine

secretion and elevated CGRP and/or VIP levels have been documented (104-106); CGRP-producing NETs secrete larger forms of calcitonin than MTC. A few patients with documented ghrelin overproduction from a pNET and a carcinoid of the stomach but without any obvious clinical symptoms and/or acromegaloid features have also been described (107;108). PNSs secondary to the ectopic production of other gut peptides, although relatively rare, are increasingly being described. Gastrin-releasing peptide (GRP) is present in highest concentration in SCLCs and, besides gastrin hypersecretion, may act as an autocrine growth factor (109). Glucagon-like peptides (GLP) 1 and 2 are derived from the post-translational processing of pro-glucagon that influence intestinal motility and small bowel growth, respectively (110). A case of a GLP-1 and somatostatin secreting NET presenting with reactive hypoglycaemia and hyperglycaemia has been described (111). Several cases of PETs and carcinoid tumours with elevated calcitonin levels associated with no clinical symptoms but causing diagnostic confusion with MTC have been described; such cases usually do not exhibit a calcitonin rise in response to pentagastrin or calcium stimulation (112;113). Human Placental lactogen (hPL) is normally produced in the latter part of gestation and stimulates the mammary gland, but has been shown to be secreted by SCLCs and phaeochromocytoma; its secretion may be associated with gynaecomastia (114). Cases of extra-renal renin-producing tumours are particularly rare, mostly related to NETs (paragangliomas and carcinoids) and SCLC leading to a hypertensive PNS (102). Other, extremely rare sporadic cases of renin-secreting tumours including desmoplastic round cell tumours (DSRCT) secreting ectopic renin (115). Cases of renin secretion from renal or pulmonary carcinomas have also been described (116). The renin-secreting tumour triad consists of hypertension, hypokalaemia and elevated plasma renin activity (PRA). Tumour resection is the therapeutic option of choice with various cases of chemo-sensitive tumours responding well to chemotherapeutic regimes. Adjuvant use of various anti-hypertensives, spironolactone or rarely aliskiren, has proven to be helpful in offering temporary symptom relief (117).

Tumour-induced osteomalacia (TIO) is a rare PNS manifested with bone and muscular pains, bone fractures, and sometimes loss of height and weight (118). The first evidence of a circulating factor that could cause phosphate wasting in humans was described when a tumour transplanted into nude mice caused hypophosphataemia (119). Fibroblast growth factor FGF-23 is secreted by the bones and was first identified as the phosphaturic agent when mutations in FGF-23 gene were linked to autosomal dominant hypophosphataemic rickets (ADHR) (120). In cases of TIO, FGF-23 (FGF-23/Klotho system) secretion is much higher leading to dysregulation of the FGF-23 degradation pathway (121). Tumours usually bearing the ability to over-secrete FGF-23 are generally of mesenchymal origin, but there are cases of an adenocarcinoma of the colon and prostate (122, 123, 124). The resolution of symptomatology in all cases involved tumour resection.

A number of mesenchymal cells can differentiate into steroidogenic cells following ectopic expression of nuclear factor (NR) 5A subfamily proteins, steroidogenic factor-1 and liver receptor homolog 1 (125). The ability of certain cells to differentiate into others may represent one of the mechanisms accounting for the development of PNS. This could be the underlying reason for the rare cases of steroid-secreting hormones leading to PNS from tissues other than the adrenal and the gonads. (125)

Paraneoplastic hyperaldosteronism has been described in a patient with ovarian cancer and also in cases of Non-Hodgkin's lymphoma (NHL) (126, 127). It has been suggested that paraneoplastic hyperaldosteronism could be secondary to the expression of the *CYP11B2* gene (127). In a patient with NHL and unexplained hypertension, RNA extraction from a lymph node demonstrated increased *CYP11B2* mRNA expression, confirming that hyperaldosteronism was paraneoplastic (127). Struma ovarii is a rare subtype of ovarian cancer representing <1% of all ovarian malignancies (128). It represents a monodermal teratoma composed of mature thyroid tissue; thyroid tissue must comprise more than 50 percent of the overall ovarian tissue to be classified as a struma ovarii. The diagnosis is usually made on clinical presentations including symptoms of overactive thyroid function. The rate of recurrence is high and in the majority of patients with malignant struma ovarii adjuvant chemotherapy is necessary. The mechanism underlying the functioning status of the tumour is still unclear, but the presence of thyroid stimulating hormone receptor (TSHr) is thought to play a role. It represents the only known malignancy that secretes ectopic TSH (128).

Cytokines

There is increasing evidence indicating that several cytokines, particularly interleukin-6 (IL-6), can be secreted directly by NETs (36). IL-6 plays an important role in the development of inflammatory reactions by stimulating the production of acute phase proteins while inhibiting albumin synthesis. A PNS presenting with fever and increased acute phase proteins has been shown to be associated with elevated IL-6 levels (30;129-131). In this context, several patients with phaeochromocytoma, pyrexia, marked inflammatory signs and elevated IL-6 levels have been described, in all of whom symptoms subsided by removal of the tumour; IL-6 expression was demonstrated in the tumours (30;132).

Neurological paraneoplastic syndromes related to NETs (Table 3)

A number of patients have been described presenting with subacute or chronic proximal muscle weakness, mainly of the pelvic and shoulder girdle muscles, and more rarely involvement of the cranial nerves, that may improve with movement. These patients has been shown to suffer from the Lambert-Eaton myasthenic syndrome (LEMS), an uncommon presynaptic neuromuscular junction disorder where voltage-gated calcium channels, which function in the release of acetylcholine from presynaptic sites, particularly the P/Q-type, are the targets of antibodies produced by the tumour cells (46). More than 50% of well-documented cases of Eaton-Lambert syndrome have been reported in association with SCLC (46). A very few cases of LEMS in association with atypical carcinoid tumours that remitted following successful treatment have been described (133). Patients may also present with an ataxic gate, loss of coordination, dysarthria and nystagmus, all symptoms suggestive that are suffering from the paraneoplastic cerebellar degeneration (PCD) syndrome (134;135). This PNS has mainly been linked to SCLCs and its pathogenesis relates to autoantibody-induced destruction of Purkinje cells (134). Very few cases of other non-SCLC NET related paraneoplastic cerebellar degeneration cases have been described (136). Limbic encephalitis is a multifocal inflammatory disorder characterised by personality

changes, irritability, memory loss, seizures and, in some cases, dementia (137). Recently, a case of limbic encephalitis associated with a thymic carcinoid has been reported (137).

Since it is expected that the incidence of NETs will increase as a result of a real increase in cases or as more cases being readily diagnosed due to physician awareness and better diagnostic tools available it is likely that the incidence of PNSs related to these tumours will also increase. It is therefore important to identify and register such cases to develop evidence based diagnostic and therapeutic guidelines.

SUMMARY

PNSs are commonly encountered in patients with NETs reflecting their multipotent potential and ability to synthesize and secrete biologically active substances and/or autoantibodies that can cause distinct clinical syndromes. These syndromes may precede the development of the tumour and their presence along with measurement of the responsible compound can be used as means to monitor response to treatment and disease recurrence. The majority of these syndromes are related to the production of peptidic mainly hormones that cause symptoms mimicking the clinical syndromes produced by the eutopic secretion of these substances. As the incidence of several types of neoplasms and in particular NETs increases, and as these patients live longer, the incidence of PNS will most probably increase. It is expected that with the identification of new compounds currently unrecognized clinical syndromes will be attributed to the secretion of such compounds.

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