PARANEOPLASTIC SYNDROMES RELATED TO NEUROENDOCRINE TUMORS

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ABSTRACT

Neuroendocrine neoplasms (NENs) are rare tumors that display marked heterogeneity with varying natural history, biological behavior, response to therapy and prognosis. Their management is complex, particularly as some may be associated with a secretory syndrome, and is undertaken in the context of a multidisciplinary team including a variety of surgical and medical options. The term paraneoplastic syndrome (PNS) is used to define a spectrum of symptoms attributed to the production of biologically active substances secreted from tumors not related to their specific organ or tissue of origin and/or production of autoantibodies against tumor cells. The majority of these syndromes is associated with hormonal and neurological symptoms. Currently, no specific underlying pathogenic mechanism has been identified although a number of plausible hypotheses have been put forward. PNSs can precede, occur concomitantly or present at a later stage of tumor 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. Clinical awareness and the incorporation into clinical practice of ^{68}Ga-labelled somatostatin analogue positron emission tomography, and other evolving biomarkers have substantially contributed to the identification of patients harboring such syndromes. When associated with tumors of low malignant potential PNSs usually do not affect long-term outcome. Conversely, in cases of highly malignant tumors, endocrine PNSs are usually associated with poorer survival outcomes. The development of well-designed prospective multicenter trials remains a priority in the field in order to fully characterize these syndromes and provide evidence-based diagnostic and therapeutic protocols.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare tumors with an estimated annual incidence of approximately 3-5 cases /100,000 inhabitants. Due to increased utilization of modern more sensitive diagnostic tools their incidence has risen over time (1,2). NENs are

predominately located in the gastrointestinal and bronchopulmonary systems but may rarely arise in other organs such as the ovaries or the urinary bladder (3). They display marked heterogeneity with varying natural history, biological behavior, response to treatment and prognosis. In general, NENs exhibit a relatively indolent course but can develop metastases and a subset can display an aggressive behavior. They are derived from cells that have the ability to synthesize and secrete a variety of metabolically active substances that are related to distinct clinical syndromes. These secretory products are characteristic of the tissue of origin and secretory tumors are denoted “functioning”. This distinguishes them from tumors originating from cells which do not produce any substances associated with recognized clinical syndromes or produce biologically inactive substances that do not have any clinical consequences. The latter tumors are called “non-functioning” and can cause symptoms, along with functioning tumors, due to mass effects and compression of surrounding vital structures (4). The non-specific immunohistochemical markers chromogranin A (CgA) and synaptophysin have been used to establish the neuroendocrine nature of these tumors and in this context tumors expressing these markers are classified as NENs (Table 1) (1,5,6). According to the proliferative index (PI) Ki-67, defined by immunohistochemical staining for nuclear Ki-67 protein expression, gastro-entero-pancreatic NENs (GEP-NENs) are classified into grade 1 (G1) or 2 (G2) if Ki-67 PI is ≤2 or between 3 and 20% respectively and grade 3 (G3) if Ki-67 PI is > 20% (7,8). Recently, the degree of tumor differentiation has been taken into consideration, and the proposed World Health Organization (WHO) classification of 2019 divided all the GEP-NENs into well-differentiated G3 neuroendocrine tumors (G3 NETs) and poorly-differentiated neuroendocrine carcinomas (G3 NECs). This distinction is of clinical significance as it correlates with the clinical behavior, the response to treatment and the overall prognosis (9,10) (Table 1). Lung NENs classification by the WHO on the contrary, is not based on Ki-67 but on mitotic counts and assessment of necrosis (11). Thus, they are classified into four histological variants, namely typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC).

Table 1. Classification of Gastro-Entero-Pancreatic Neuroendocrine Neoplasms (WHO 2019)

	Ki67 index (%)	Mitotic Index
Well Differentiated NENs		
Neuroendocrine Tumor (NET) G1	< 3	< 2/10 HPF
Neuroendocrine Tumor (NET) G2	3-20	2-20/10 HPF
Neuroendocrine Tumor (NET) G3	> 20	> 20/10 HPF
Poorly Differentiated NENs		
Neuroendocrine Carcinoma (NEC) G3	> 20	> 20/10 HPF

HPF= high-power field

More than 100 years ago, it was recognized that patients with malignant tumors may develop symptoms that cannot be attributed to direct tumor invasion/compression or to a clinical syndrome associated with a secretory product derived from the specific cell of origin (12). The term paraneoplastic syndrome (PNS) was first described in 1940s and is used to define a spectrum of symptoms attributed to the production of hormones, growth factors, cytokines and/or other substances by the tumor cells not

designated to release these specific compounds or as of consequence of immune cross-reactivity between tumor and normal host tissues (13). In some instances, these syndromes are caused by the secretory products, mainly peptide hormones, of neuroendocrine cells that are widely dispersed throughout the lung, gastrointestinal (GI) tract, pancreas, thyroid gland, adrenal medulla, skin, prostate and breast (1,14). 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 (12).

It has been estimated that PNSs affect approximately 8-15% of patients suffering from malignant neoplasms, mostly involving the lung, breast, and gastrointestinal system (13-17). NENs are the type of tumors that are expected to exhibit the highest prevalence of PNSs due to their inherent synthetic and secretory capacity. However, to date the prevalence of NEN-related PNSs is still obscure due the limited availability of data (16,18-21). Following the continuing rise in the prevalence of NENs and the significant application of the available diagnostic modalities, it is expected that the prevalence of PNSs related to NENs will also rise (1,22).

A PNS can develop during different phases of the evolution of the neoplastic process. It can present before the diagnosis of the underlying malignancy and help making the diagnosis of a previously unsuspected neoplasm at an early disease stage (5,23). Furthermore, the presence of a PNS and the related etiological factor may be useful in following the clinical course of the disease, in monitoring the response to treatment, and/or detecting early recurrence of the neoplasm (16,17). Effective and prompt diagnosis and treatment of the PNS may substantially improve overall clinical outcomes. However, the development of a PNS does not always correlate with the stage of the disease, the malignant potential of the tumor and the overall prognosis. Furthermore, in the presence of highly aggressive tumors or extensive disease burden, management of these syndromes may be difficult (5,24).

It is therefore critical to recognize the presence of a PNS and to record common and uncommon cases related to NENs in order to provide further information regarding the clinical manifestations, the natural history and the overall prognosis and improve the clinical outcome of the patients.

CLASSIFICATION

According to the clinical manifestations, the NENs-related PNSs may be classified as (5):

- Humoral PNSs
- Neurological PNSs
- Other less common manifestations

PATHOGENESIS

Although several hypotheses have been proposed regarding the pathogenesis of PNSs, the precise mechanism that leads to the development of PNS remains largely unknown. All human cells carry the same genetic information of which only part is expressed through their life span. Neoplastic transformation is linked to alterations of oncogenes, tumor suppressor genes, and apoptotic mechanisms that control cell growth (17,25). In addition, under certain conditions specific alterations of gene functions may activate genes that regulate hormonal synthesis, particularly in the context of an underlying neoplastic process, leading to the development of a PNS. Inappropriate gene expression heralds the unscheduled appearance of a gene product in a non-designated tissue or organ leading to a PNS, as encountered in many different animal species (23). Similar underlying mechanisms may operate to initiate a PNS, 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 (16,17). However, the exact mechanism that initiates ectopic hormonal synthesis

and release at a specific time point during the neoplastic transformation still remains to be elucidated.

Ectopically produced substances are mostly peptides or glycoproteins while rarely biogenic amines, steroids and thyroid hormones are associated with the development of a PNS (5,24). The clinical manifestations are produced as a result of the direct secretion of these substances from the tumor, arising from tissue other than the endocrine gland or tissue that normally produces them, to the circulation. On top of this, the secreted products may also exert paracrine and autocrine effects. The term 'ectopic hormonal production' leading to a PNS is used whenever these compounds are secreted in such proportion that may be related to clinical manifestations and are found in large quantities in the serum (14,26). In some instances, the synthesis and/or processing of these substances in malignant tissues may be different from that of the eutopically-secreted hormone (27). In addition, it has recently been observed that a minority of patients with pancreatic NENs multiple hormone secretion was detected at diagnosis and alteration of the hormonal secretion may be observed during the disease course (28).

PNSs may also develop secondary to antibody formation induced by the expression of antigens, usually expressed in neuronal tissue, by some neoplasms. The recognition of antigens in neuronal tissues by these antibodies leads to the development of neurological symptoms (5).

DIAGNOSIS

The wide application of modern diagnostic modalities has contributed immensely to the identification and characterization of PNSs derived from NENs. It is important for physicians to be familiar with the clinical presentation of a PNS as well as with the imaging modalities and the laboratory tests that would allow the prompt and effective diagnosis and treatment.

In order to qualify a spectrum of symptoms as a PNS several clinical, biochemical and histopathological criteria have to be fulfilled (Table 2). In the context of a specific clinical syndrome, the demonstration of increased levels of a humoral compound in the circulation along with in situ hybridization to detect the specific substance's mRNA and immunohistochemistry to demonstrate its protein presence in the tumor tissue, provide the evidence for diagnosing a PNS (12,17). It has to be noted that in some cases, molecular forms different form a eutopically produced compound may be secreted in the circulation while endocrine dynamic function tests may also be required to prove the ectopic secretion of a substance (12,17). Furthermore, a number of autoantibodies have been shown to be of diagnostic significance in neurological PNSs (5).

Table 2. 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 tumor and the arterial level of the same product
• **Histopathological** Presence of bio/immuno-reactive and relevant mRNA of the secretory product in tumor tissue Synthetic and secretory ability of the product by tumor cells in vitro

General circulating biomarkers associated with NENs include CgA and neuron specific enolase (NSE) while there are multiple studies investigating the role of several biomarkers as well as of genetic and epigenetic alterations, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), histone modifications, mRNA transcripts (NeTest), and miRNAs, as prognostic factors and predictors of response to treatment (29-31)

Conventional imaging modalities such as computerized tomography (CT), magnetic resonance imaging (MRI), colonoscopy, gastroscopy, and endoscopic ultrasound (EUS) are used for detection of the primary tumor and metastatic lesions (8,32). As the majority of NENs express high levels of somatostatin receptors (SSTRs), these neoplasms can also be detected with somatostatin receptor imaging by ^{111}In-labelled scintigraphy (SRS; Octreoscan or Tektrotyd) or by ^{68}Ga-labelled positron emission tomography (PET; ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET/CT) that allow whole body scanning. 68Ga-laballed somatostatin analogue PET/CT has been proved to be the most sensitive method for the diagnosis and staging of NENs (Figure 1) (32). Furthermore, ^{18}F-fluorodeoxyglucose (FDG) PET/CT is a whole body imaging procedure that assesses glycolytic metabolism and has higher sensitivity than SRS in G3 tumors (8,32).

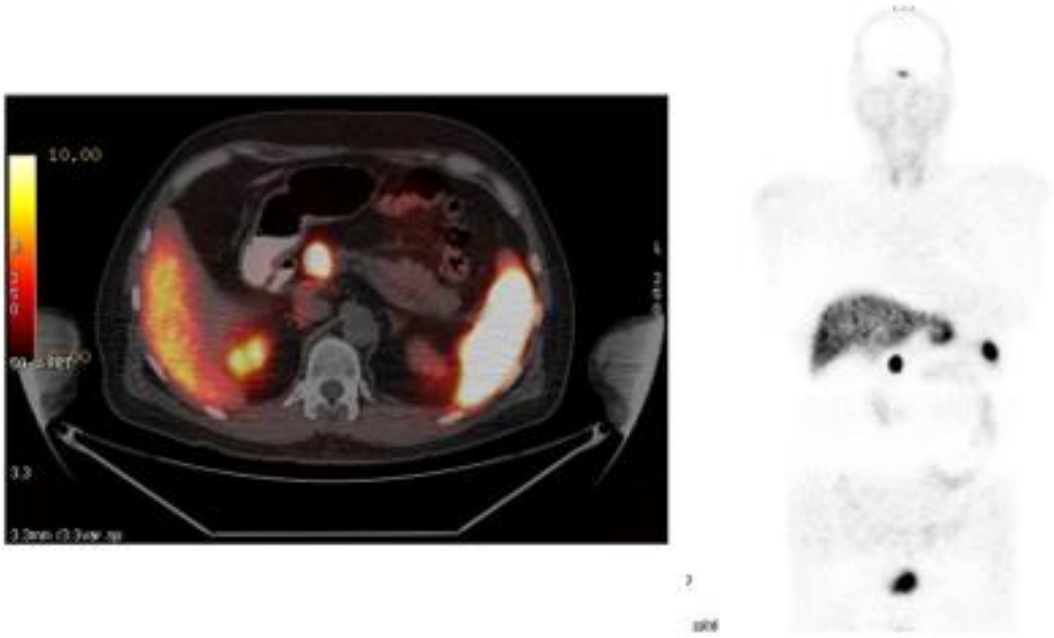

Figure 1. Increased uptake of a pNEN in ^{68}Ga-PET/CT; pNEN: pancreatic neuroendocrine neoplasm; ^{68}Ga-PET/CT: ^{68}Ga DOTATOC Positron emission tomography/computed tomography

HUMORAL PARANEOPLASTIC SYNDROMES IN NENs

Hypercalcemia

Humoral hypercalcemia is one of the commonest PNSs that occurs in up to 10% of patients with advanced malignancies and is associated with a poor prognosis as the 30-day mortality can be up to 50% (33,34). In the absence of osseous metastases and parathyroid gland disease, hypercalcemia in cancer patients may be caused from ectopic secretion of parathyroid hormone (PTH), 1,25 dihydroxy-vitamin D3, or PTH-related protein (PTHrP) (5,24).

The vast majority (>80%) of NEN-related hypercalcemia is secondary to the ectopic secretion of PTHrP (24,35). PTHrP was first isolated in 1987 from cancer cell lines and a tumor associated with hypercalcemia. It is considered to be the most common cause of humoral hypercalcemia of malignancy (36,37). It binds to PTH receptor as well as to other receptors and exerts effects other that PTH on tissues such as the skin, the breast, and the anterior pituitary (34,35). Hypomethylation of the *PTHrP* promoter has been implicated as a mechanism of its aberrant gene expression (37).

The first case of a PTHrP-producing malignant NEN was observed in a patient presenting with a pancreatic NEN (pNEN) and severe hypercalcemia during pregnancy (38). Since then, several reports have been published that describe patients with metastatic NENs presenting with biochemical and/or immunohistochemical PTHrP-related hypercalcemia (21,39). A recent retrospective case series reported that hypersecretion of PTHrP by metastatic GEP-NENs is a rare event that seems to be exclusively associated with metastatic pNENs (20). Interestingly, a case of a brown tumor in a patient with long-standing PTHrP related hypercalcemia has been described confirming the relevant biological homology of this peptide to the native hormone (40). Despite the fact other PTHrP-secreting neoplasms display a poor prognosis, patients with NEN-related PTHrP production have a much better outcome (39). In addition, there are cases of benign pheochromocytoma that have been associated with PTHrP-related hypercalcemia (41).

Very few cases of ectopic PTH secretion from NENs have been documented mainly from SCLCs, pheochromocytoma, and MTC (42-44) . A case of PTH-related hypercalcemia in a patient with metastatic poorly differentiated small-cell pNEC has also been described (45). There is a recent report of hypercalcemia observed in a patient with glucagon cell hyperplasia and neoplasia (Mahvash Syndrome) but the exact pathophysiology of hypercalcemia in this case remains unclear since PTH, PTHrP, and 1,25 dihydroxy-vitamin D3 were low. Activation of the calcium sensing receptor by the hyperaminoacidemia or the concurrently found increased levels of glucagon-like 1 peptide (GLP-1) could contribute to the hypercalcemia through an undefined mechanism (46).

Clinical manifestations of hypercalcemia include nausea, vomiting, polyuria, constipation cognitive dysfunction and coma (47). Symptom severity depends not only on the degree of hypercalcemia but also on the rapidity of onset and the patient's baseline renal function. In patients with PTHrP-related hypercalcemia, typical laboratory findings include increased calcium levels, low phosphate levels, low or inappropriately normal PTH, and increased PTHrP and nephrogenous cAMP levels (5,24). The optimal management of paraneoplastic hypercalcemia is treatment of the underlying tumor. It has been observed that the most successful treatment options for PTHrP-producing GEP-NENs are long acting

somatostatin analogues (SSAs) and peptide receptor radionuclide therapy (PRRT) using radiolabeled SSAs whereas multiple anti-tumors modalities may be required to control cases of refractory hypercalcemia in inoperable patients (20). However, in severe cases, medical treatment of hypercalcemia according to recent guidelines may also be required (47,48). Intravenous administration of zoledronic acid is superior to pamidronate for patients with malignancy associated hypercalcemia, including humoral causes(49). Denosumab can be considered in bisphosphonate-refractory disease(50). On top of this, the calcimimetic cinacalcet and the tyrosine kinase inhibitor (TKI) sunitinib that has been observed to cause hypocalcemia may be effective in treating NEN-related hypercalcemia (51) (52).

Ectopic Vasopressin & Atrial Natriuretic Peptide Secretion

Vasopressin (ADH) is produced within the hypothalamus and stored in nerve terminals of the posterior pituitary as well as in a subset of neuroendocrine cells in the lung (53). Additional processing can also occur in SCLC cells and other neoplasms that can also synthesize and secrete oxytocin (5). The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) was first described in the early 1950s. It is characterized by hypo-osmotic, euvolemic hyponatremia in the absence of plasma hypotonicity and occurs in 1-2% of all patients with malignant tumors (54,55). Atrial natriuretic peptide (ANP) is synthesized from the cardiac atria and can initiate natriuresis and hypotension when ectopically produced by NENs (56,57). However, severe cases of hyponatremia are mostly associated with SIADH (5).

SIADH is most commonly found in SCLCs, while cases of large cell lung carcinomas (LCLCs) have also been reported (54,58,59). Although vasopressin levels are increased in up to 50% of patients with SCLCs, only 15% of patients develop the syndrome (60). In addition, SIADH has been observed in rare cases of sinonasal NEC, pNEC, small cell rectum NEC and NEC of the uterine cervix (61-64). Recently, a patient with a grade 1 insulinoma has been reported that developed SIADH during the disease course and after disease progression (65). Immunohistochemical examination of the tumor tissue at autopsy was diffusely positive for vasopressin while the initial tissue biopsy was negative for vasopressin. In addition, there are some rare reports of patients with SCLC secreting both ACTH and ADH. They tend to have more extensive disease and are more likely to have a poor prognosis, with a survival time of 2-4 months after the diagnosis, because the disease is refractory to treatment. Interestingly, ectopic adrenocorticotropic hormone (ACTH) secretion may mask SIADH due to the antagonistic action of cortisol and ADH on renal sodium excretion (66,67).

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 (68). 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 (68). In SCLC, SIADH has been associated with a higher propensity for central nervous system metastases, poor response to chemotherapy and advanced stage of cancer (59). The grade of hyponatremia at short-term follow-up was also predictive for long-term survival (69). There appears to be no clinical and/or biochemical features distinguishing the origin of the tumor although most severe symptoms are encountered in patients with highly aggressive tumors (70).

Treating the underlying neoplasm is the best means of correcting the hyponatremia (71). In the absence of symptoms, gradual correction of the hyponatremia is appropriate and involves adequate solute intake and fluid restriction (71,72). 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 (71). 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 (72,73). Tolvaptan is hepatotoxic and should not be used in patients with liver disease. Intravenous conivaptan is very effective in correcting hyponatremia and baseline mental status in hospitalized patients (74,75). It has recently been shown that prompt endocrine input improved time for correction of hyponatremia and shortened length of hospitalization, and the widespread provision of endocrine input should be considered (75-77).

Cushing's Syndrome (CS)

The ectopic Cushing’s syndrome (ECS) that develops secondary to the secretion of ACTH and less often of corticotrophin-releasing hormone (CRH) by non-pituitary tumors comprises 10%-20% of ACTH-dependent CS and 5-10 of all types of CS(78-81).

In a recent study looking at a large cohort of patients with NENs, the reported prevalence of ECS was 1,9% (21). NENs associated with ectopic ACTH secretion are mainly derived from the lung (bronchial carcinoids, SCLC and rarely LCLC), thymus, pancreas, thyroid (MTC), chromaffin cell tumors (pheochromocytomas, paragangliomas, neuroblastomas), and rarely from the ovary or prostate(79,82-86). Bronchial carcinoids (3–55%), are the most frequent causes of ectopic ACTH secretion in more recent series, whereas SCLC represented the most common tumor associated with ECS in early series (3–50%)(18,25,79,87). Ferreira et al, have recently reported a case of an aggressive MTC that produced both ACTH and serotonin (88). Unknown primary tumors account for 12–37% of all causes of ectopic ACTH production (89). In the majority of cases, these occult tumors are located in the lung and ACTH-secreting lung carcinoids or carcinoid tumourlets as small as 2-3 mm have been documented (79,90). However, other rare sites such as the appendix have also been described (91,92).

Rarely ECS may result from CRH production from SCLCs, MTCs, carcinoids, pNENs, and pheochromocytomas accounting for approximately 5% of all cases of ECS (81,84,93,94). Such patients have high CRH levels in plasma and tumor tissue whereas plasma ACTH levels are also increased. CS due to CRH production does not have a distinctive presentation and endocrine testing may resemble an interplay between ectopic and eutopic production. In addition, there are some rare reports of ECS associated with NENs secreting both CRH and ACTH(95,96).

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 (97). Large amounts of biologically active ACTH are found in tumor tissue, although immunoreactive ACTH may also be found at high concentrations in tumor extracts from patients without clinical manifestations of CS (5). In addition, up to 30% of SCLCs hypersecrete ACTH that may be bio-inactive following incomplete processing and thus not capable of inducing a clinical syndrome (89,98). Using bisulphite sequencing and hypomethylation in five thymic carcinoid tumors resected from patients with ectopic ACTH syndrome, its presence correlated with POMC over-expression and the ectopic ACTH syndrome (97). 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 (27).

The clinical manifestations of ECS display significant heterogeneity according to the severity of hypercortisolism and the malignant potential of the underlying tumor. Lung carcinoids, thymic carcinoids and pheochromocytomas cause the ‘indolent’ type of

ECS exhibiting gradual onset of typical symptoms and signs of CS resembling Cushing's disease (99). SCLC, pNENs, malignant pheochromocytomas, thymic carcinomas, and MTCs are associated with an 'aggressive' type of ECS caused by very high ACTH and cortisol levels and present with rapid onset of clinical signs and symptoms including weight loss, hyperpigmentation, hypertension, hypokalemia, diabetes mellitus, and psychiatric alterations (99). The time interval between the appearance of the first symptoms of ECS and the diagnosis of the tumor is approximately 3–4 months for SCLCs, 6–8 months for pNENs and 6-24 months for lung carcinoids (99). However, there is a considerable overlap between these two types of ECS and could be viewed as a continuum rather than two different types. In rare instances, cyclic ACTH secretion may render the diagnosis extremely difficult. Cyclic ECS characterized by episodes of hypercortisolism interspersed with phases of normal cortisol production or adrenal insufficiency, is usually associated with indolent tumors and its long-term course may be variable (100-103). There are some reports of spontaneous remission of ECS after treatment with steroidogenesis inhibitors but it is unknown whether medical treatment played any role in the resolution of hypercortisolism (100,101).

The discrimination between ECS and Cushing's disease may be quite challenging as both pituitary tumors and lung carcinoids are often small in size and difficult to detect. It has been suggested that no single endocrine test and/or imaging procedure are accurate enough to diagnose and localize ectopic ACTH/CRH-producing tumors, particularly as false positive inferior petrosal sinus sampling (IPSS) results may occasionally be obtained, albeit very rarely (5,104,105). Frete et al, have recently proposed a non-invasive diagnostic strategy in ACTH-dependent CS in order to decrease the requirement of IPSS using the combination of CRH and desmopressin tests along with pituitary MRI and thin-slice whole-body CT scan, a protocol that was associated with 100% positive predictive value for Cushing's disease (106). However, small ectopic sources may still contain many of the intrinsic regulatory mechanisms of corticotroph tumors and respond to endocrine testing making the differential diagnosis really challenging. Hence, the IPSS remains the gold standard test to identify a pituitary versus ectopic source of ACTH as it is associated with sensitivity and specificity > 95% (78,107). In case of confounding results, ^{68}Ga-labelled somatostatin analogue PET/CT has been proved to be a sensitive functional imaging study that identifies occult tumors after conventional imaging and impacts clinical care in the majority of patients (108).

The management of ECS relies on successful control of the underlying malignancy and treatment of comorbidities. The ideal treatment is complete excision of the ACTH-secreting tumor that can be performed rapidly or after preoperative preparation using cortisol-lowering drugs (109). Ketoconazole and metyrapone are used as first line treatment due to their efficacy and safety, while the glucocorticoid receptor antagonist mifepristone, dopamine agonists, and SSAs have also been shown to be effective in small series (78,110-112). When rapid correction of the hypercortisolism is required intravenous etomidate can be used (113). Occasionally hypercortisolism may be extremely severe and difficult to control with adrenolytic medication, necessitating bilateral adrenalectomy (109).

In a study of 29 patients with ECS related to thoracic or GEP-NENs the median overall survival (OS) was 41 months. However, only the first 5-year survival of patients with ECS was shorter compared to patients with no ECS (18). Daskalakis et al, showed that patients with ECS of extra-thoracic origin demonstrated shorter OS compared to patients with ECS of lung or thymic origin while patients with lung carcinoids displayed comparable 5-year and 10-year OS rates irrespectively of the presence of ECS (21). Multiple factors affect the prognosis of patients with ECS. A recent retrospective analysis of 110 patients suffering from NENs and ECS found that OS was significantly higher in lung carcinoids compared with

pNENs and occult tumors and in G1 NENs compared with G2 and G3 (90). Negative predictive factors for survival were the severity of hypercortisolism and the presence of hypokalemia, diabetes mellitus, and distant metastases. Improved survival was observed in patients who underwent surgical removal of the NEN, while adrenalectomy improved short-term survival. Furthermore, a retrospective study of 886 patients with NENs found that in patients with ECS multiple hormone secretion was associated with shorter OS (114).

Acromegaly

Acromegaly secondary to non-pituitary tumors is rare and accounts for less than 1% of cases of acromegaly. Ectopic acromegaly is mostly related to growth hormone-releasing hormone (GHRH)-hypersecretion and rarely to growth hormone (GH) itself (63,115,116). NENs most commonly associated with GHRH hypersecretion are bronchial and thymic carcinoids, pNENs, SCLCs, and pheochromocytomas. A few patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome and GHRH-producing pNENs have also been described (116-122). Ectopic GH secretion from NENs has been rarely reported, whereas. a case of acromegaly and CS caused by a NEN arising within a sacrococcygeal teratoma has recently been described (123,124).

Clinical presentation is not different to that of pituitary origin while biochemical findings are also similar in both pituitary-related and ectopic acromegaly, characterized by elevated insulin-like growth factor 1 (IGF1) and GH levels, with the latter failing to suppress following an oral glucose tolerance test (OGTT). Serum GHRH has been proposed as a useful diagnostic tool which could be used as a marker for disease activity or tumor recurrence (125). Pituitary imaging is not always helpful in differentiation between pituitary-related and ectopic acromegaly. Normal pituitary or uniform pituitary enlargement are the expected findings in cases of ectopic acromegaly. However, in a recent review of 63 pituitary MRIs in patients suffering from ectopic acromegaly, 13 cases were reported as pituitary adenoma, highlighting the importance of MRI evaluation by an experienced radiologist (125).

Treatment of ectopic acromegaly is mainly surgical and involves resection of the responsible tumor either with a curative intent or as debulking surgery. When surgical treatment is not feasible or in case of metastatic disease, SSAs can also be useful for the treatment of the tumor and the biochemical control of acromegaly (4,126).

Hypoglycemia

Tumor-associated or paraneoplastic hypoglycemia occurs rarely and is caused by insulin-producing non islet-cell tumors and tumors secreting substances that can induce hypoglycemia by non-insulin mediated mechanism, a condition called non-islet cell tumor hypoglycemia (NICTH) (127,128). 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″ (127,129). This molecule has a molecular mass of 10-17 kDa, that is substantially bigger than the 7.5 kDa mature IGF2. This structure has substantially reduced affinity to its cognate binding protein, 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 hypoglycemia; IGF1 levels are usually also low (130,131). The confirmation of the diagnosis is not often given by a high level of IGF-2 but by a high IGF-2: IGF-1 ratio. A ratio greater than 10:1 is highly suggestive of IGF-2 precursor secretion (131). Although “big-IGF2” is mostly secreted by tumors of mesenchymal and epithelial origin, rare cases of NENs and pheochromocytomas have also been described (5,131,132). The diagnosis should always be suspected in patients presenting with hypoglycemic symptoms, particularly in the presence of a malignant tumor. Acromegalic skin changes have also been described in patients with NICTH(133).

The possibility of hypoglycemia due to insulin secretion from non-islet-cell tumors is controversial and a few cases have been described. Furrer et al, have described a primary NEN of the liver that manifested initially as extrapituitary acromegaly and a typical carcinoid syndrome, and later on as a hyperinsulinemic hypoglycemic syndrome (134). Li et al, reported a case of ectopic insulinoma in the pelvis secondary to rectum neuroendocrine tumor (135). In addition, a few cases of insulin-secreting NENs of the cervix, ovaries and kidney and paragangliomas have also been described (136-139). A rare case of a LCLC with recurrent hypoglycemia, low insulin and big IGF2 levels and increased IGF1 levels has also been described, while there are reports of somatostatinomas or GLP-1 secreting tumors that caused hypoglycemia (140-142).

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 tumor; even partial removal often may reduce or abolish the hypoglycemia (143). Both human GH and glucocorticoids can induce a substantial effect while SSAs can also be used with caution as they can inhibit the secretion of counter-regulatory to hypoglycemia hormones (4,144,145). 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 (146). It appears that either IGF-2 does not cause hypoglycemia 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 (146).

Ectopic Secretion of Other Peptidic (Including Pituitary) Hormones

Although extremely rare, a few cases of ectopic luteinizing hormone (LH) production from pNENs have been described (147,148). No definite case of ectopic TSH has clearly been described, whereas ectopic prolactin production has been reported in association with SCLCs (4,16,94,149). Tumor-associated β-human chorionic gonadotrophin (β-hCG) production has been demonstrated in SCLCs and pNENs clinically associated with gynecomastia in men, menstrual irregularity and virilization in women and precocious puberty in children (94). A case report of a boy with severe arterial hypertension and hyperandrogenism due to ectopic secretion of β-hCG by a pheochromocytoma has been recently published (150). 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 pheochromocytomas; its secretion may be associated with gynecomastia (151). Ectopic renin secretion is extremely rare and has been described in a SCLC, paraganglioma, and a carcinoid tumor accompanied by hypertension and hypokalemia. An increased ratio of pro-renin to renin is found due to inefficient processing of renin by the tumors (152,153). A few cases of ectopic production of vasoactive intestinal polypeptide (VIP) causing watery diarrhea arising from a SCLC, MTC, and a pheochromocytoma have been described (154,155). Several cases of pheochromocytomas presenting with flushing, hypotension or normal blood pressure in the context of excessive catecholamine secretion and elevated calcitonin gene-related peptide (CGRP) and/or VIP levels have been documented (156-158). CGRP-producing NENs secrete larger forms of calcitonin than MTC. A few patients with documented ghrelin overproduction from a pNEN and a carcinoid of the stomach but without any obvious clinical symptoms and/or acromegalic features have also been described (159,160). 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 (161). A case of a GLP-1 and somatostatin secreting NEN presenting with reactive hypoglycemia and hyperglycemia has been reported (142). Several cases of pNENs and carcinoid tumors 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 (162,163). In addition, increased secretion of calcitonin has been detected in a case with a metastatic esophageal NEN (164).

Tumor-induced osteomalacia (TIO) is a rare PNS manifesting with bone and muscular pains, bone fractures, and sometimes loss of height and weight(165). The first evidence of a circulating factor that could cause phosphate wasting in humans was described when a tumor transplanted into nude mice caused hypophosphatemia (166). 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 hypophosphatemic rickets (ADHR) (167). In cases of TIO, FGF-23 secretion is elevated leading to dysregulation of the FGF-23 degradation pathway (168). Tumors 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 (169-171). Although to date there is no direct association of this PNS with NENs, its presence has for the most part not been actively sought.

Cytokines

There is increasing evidence indicating that several cytokines, particularly interleukin-6 (IL-6), can be secreted directly by NENs (172). 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 (172-174). In this context, several patients with pheochromocytoma, pyrexia, marked inflammatory signs and elevated IL-6 levels have been described. In all of these patients symptoms subsided by removal of the tumor while immunohistochemical IL-6 expression was demonstrated in the tumors (175,176).

NEUROLOGICAL PARANEOPLASTICSYNDROMES RELATED TO NENS (TABLE 3)

Immune-mediated PNS may develop in less than 1 in 10.000 patients with cancer (177). The frequency of neurological PNSs in patients with NENs is unclear but may range from 0.01% to 8% of patients (178).

Table 3: Neurological and Dermatological Paraneoplastic Syndromes and Responsible Autoantibodies Related to NENs						
Neurological PNSs	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	-
NEN	SCLC, carcinoid	SCLC	SCLC, carcinoid	SCLC	SCLC	SCLC, carcinoid
Dermatologic PNSs	Scleroderma-like	Palmar fasciitis	Flushing-Rosacea	Dermatomyositis	TEN-like syndrome	Pellagra
NEN	SCLC, carcinoid	SCLC	SCLC, carcinoid	SCLC	SCLC	SCLC, carcinoid

PNSs: Paraneoplastic Syndromes, NEN: Neuroendocrine Neoplasms, SCLC: Small cell lung carcinoma, TEN-like: Toxic Epidermal Necrolysis-like syndrome

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 have been shown to suffer from the Lambert-Eaton myasthenic syndrome (LEMS), an uncommon presynaptic neuromuscular junction disorder. In this disease, antibodies produced by the tumor cells target voltage-gated calcium channels, which function in the release of acetylcholine from presynaptic sites, particularly the P/Q-type (57). More than 50% of well-documented cases of Eaton-Lambert syndrome have been reported in association with SCLC (57). A few cases of LEMS have been described in association with atypical carcinoid tumors and these remitted following successful treatment (179). 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. This PNS has mainly been linked to SCLCs and its pathogenesis relates to autoantibody-induced destruction of Purkinje cells (180,181). A few cases of other non-SCLC NEN related paraneoplastic cerebellar degeneration cases have been published (182). Limbic encephalitis is a multifocal inflammatory disorder characterized by personality changes, irritability, memory loss, seizures and, in some cases, dementia (183). Recently, two cases of limbic encephalitis associated with a thymic carcinoid and an anorectal small cell NEC have been reported (183,184).

Tannoury et al, published a case series of 15 patients with gastrointestinal NENs who presented with neurological symptoms and displayed no evidence of a direct link between the tumors and their symptoms (177). Most of them (85%) presented with well recognized syndromes including encephalopathy and peripheral neuropathy. Of the 6 patients whose serum antineuronal antibodies were assayed, five had high titers while the clinical syndrome improved after debulking surgery and treatment with corticosteroids and/or immunosuppressive drugs. These findings suggest that the neurological symptoms may have been related, in part at least, to immune-mediated PNS.

Other Less Common Manifestations

The association of photoreceptor degeneration and SCLC, termed cancer-associated retinopathy (CAR), has been attributed to autoantibodies produced by malignant cells that react with a 23-kDa retinal antigen termed 23-kDa CAR antigen and manifests clinically as ring scotomatous visual field loss, and attenuated arteriole caliber (185). Cases of orthostatic hypotension secondary to autonomic dysfunction and nephrotic syndrome have also been reported in patients with SCLCs and carcinoid tumors (57,186). In addition, a recently published case report described a patient with a well-differentiated duodenal NEN and nephrotic syndrome due to minimal change glomerulonephritis (187).

SUMMARY

PNSs are commonly encountered in patients with NENs 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 diagnosis of the tumor 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 hormones that cause symptoms mimicking the clinical syndromes produced by the eutopic secretion of these substances. Since it is expected that the incidence of NENs 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 it is likely that the incidence of PNSs related to these tumors will also increase. It is therefore important to identify and register such cases to develop evidence-based diagnostic and therapeutic guidelines.

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