Paraneoplastic endocrine syndromes

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Abstract

The majority of neoplasms are responsible for symptoms caused by mass effects to surrounding tissues and/or through the development of metastases. However, occasionally neoplasms, with or without endocrine differentiation, acquire the ability to secrete a variety of bioactive substances or induce immune cross-reactivity with the normal tissues that can lead to the development of characteristic clinical syndromes. These syndromes are named endocrine paraneoplastic syndromes when the specific secretory components (hormones, peptides or cytokines) are unrelated to the anticipated tissue or organ of origin. Endocrine paraneoplastic syndromes can complicate the patient’s clinical course, response to treatment, impact prognosis and even be confused as metastatic spread. These syndromes can precede, occur concomitantly or present at a later stage of tumour development, and along with the secreted substances constitute the biological ‘fingerprint’ of the tumour. Their detection can facilitate early diagnosis of the underlying neoplasia, monitor response to treatment and/or detect early recurrences following successful initial management. 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. Recent medical advances have not only improved our understanding of paraneoplastic syndrome pathogenesis in general but also enhanced their diagnosis and treatment. Yet, given the rarity of endocrine paraneoplastic syndromes, there is a paucity of prospective clinical trials to guide management. 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.

Introduction

The term paraneoplastic syndrome (PNS) was first described in the 1940s when it was recognised that certain neoplasms may cause various symptoms that are not solely attributable to direct tumour invasion, compression and/or the development of metastases (Guichard et al. 1949). Such neoplasms present or acquire in time the ability to secrete a variety of biologically-active substances that can lead to the development of distinctive clinical syndromes. These syndromes are termed paraneoplastic because the secretory components responsible for their development are not derived from the anticipated organ or tissue of origin. PNS can be the product of tumour-secreted peptides,
Paraneoplastic syndromes

Paraneoplastic syndromes mostly result from the production of bioactive substances from neoplastic cells, of endocrine or neuroendocrine origin, that are widely distributed throughout the lungs, gastrointestinal tract, pancreas, thyroid gland, adrenal medulla, skin, prostate and breasts (Agarwala 1996, Modlin 2008). A distinctive feature of endocrine PNS is that related symptoms cannot be attributed to the presence of a secreting neoplastic lesion related to the originating anatomic site, and thus the secretion of peptides, amines or other bioactive substances is regarded as ectopic (Kaltsas 2010). This is particularly relevant as neoplasms without endocrine differentiation may also acquire the ability to synthesise and secrete these bioactive substances, leading to clinically similar endocrine tumour-derived PNS (Table 2).

Table 1 Criteria for defining ectopic hormonal (paraneoplastic) syndromes.

<table>
<thead>
<tr>
<th>Endocrine or metabolic disturbance in a patient with a tumour</th>
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<tr>
<td>Remission after successful treatment</td>
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<td>Return of endocrine syndrome with tumour recurrence</td>
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<tr>
<td>Abnormally regulated elevated hormone levels</td>
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<tr>
<td>Significant gradient between hormone concentration in the venous effluent from the tumour and arterial hormone levels</td>
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<td>Extracts from tumour exhibit bio- and/or immunoreactive hormone</td>
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<tr>
<td>Relevant hormone mRNA can be identified in tumour tissue</td>
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<td>Synthesis and secretion of relevant hormone by tumour cells in vitro</td>
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amines or cytokines, or immune cross-reactivity between neoplastic and normal tissues, and can originate from either endocrine or non-endocrine neoplasms (Pelosof & Gerber 2010). 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. The criteria for the diagnosis of endocrine PNS are shown in Table 1.

PNS can develop during different phases of the evolution of the neoplastic process, with an estimated prevalence of approximately 8% among all malignant neoplasms (Baijens et al. 2006). In some cases, PNS can manifest itself before the diagnosis of the underlying malignancy and may facilitate diagnosis at an early and potentially reversible disease stage (Tarin 2013). Furthermore, the presence of PNS and measurement of the related aetiological factor can be used to monitor response to treatment and/or detect recurrence of the tumour following initial successful treatment. Effective and prompt diagnosis and treatment of the PNS may substantially improve overall clinical outcomes. However, occasionally, in the presence of highly aggressive tumours or extensive disease burden, management of these syndromes may be difficult and their presence can contribute to the morbidity and mortality of the underlying disease (Kaltsas et al. 2010). 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 (Oberg et al. 2016). In the present review only endocrine PNS will be considered, excluding those related to different pathophysiological processes and/or exhibiting manifestations in other systems.

Paraneoplastic endocrine syndromes

Paraneoplastic endocrine syndromes mostly result from the production of bioactive substances from neoplastic cells, of endocrine or neuroendocrine origin, that are
Table 2  Ectopic Cushing’s syndrome (CS): differences in clinical, laboratory and radiological features compared to eutopic secretion.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mediator</th>
<th>Tumour</th>
<th>Clinical/biochemical</th>
<th>Endocrine testing</th>
<th>Radiological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s syndrome (CS)</td>
<td>ACTH and (rarely) CRH</td>
<td>SCLC</td>
<td>Hypokalaemia/cachexia</td>
<td>↑ ACTH (isoforms)</td>
<td>Pituitary MRI (−)</td>
</tr>
<tr>
<td>Carcinoid tumour</td>
<td></td>
<td>Carcinoid tumour</td>
<td>Cushingoid phenotype</td>
<td>HDDSST (−), CRH (DDAVP test) (−)</td>
<td>BIPSS (−)</td>
</tr>
<tr>
<td>Thymus, mediatinum</td>
<td></td>
<td>Thyroid (MTC)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pheochromocytoma</td>
<td></td>
<td>Abdomen (paraganglioma, ovary, other)</td>
<td></td>
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</tr>
</tbody>
</table>

Prompt endocrine PNS recognition may facilitate the diagnosis of an underlying unsuspected neoplasm, avoid extensive investigations to identify a presumptive eutopic hormonal-secreting neoplasm, and will allow for the monitoring of the clinical course and response to treatment of the underlying tumour (Pierce 1993, Bollanti 2001).

**Pathogenesis**

Although several attractive hypotheses have been proposed for the pathogenesis of endocrine PNS, the exact events that lead to their development are still elusive (Spinazze et al. 2006). It is well known that 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 endocrine PNS (Granot & Fridlender 2015). 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 (Tarin 2013). 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 (Kaltsas et al. 2010).

Ectopically produced bioactive substances from endocrine and non-endocrine neoplasms leading to endocrine PNS are mostly peptides and hormones, and less commonly biogenic amines, steroids or thyroid hormones (Kaltsas et al. 2010, Dimitriadis et al. 2016). The symptoms are produced following the direct secretion of these substances from the tumour to the circulation, although they may also exert paracrine and autocrine effects. When symptoms develop, ectopically related hormones are found in large quantities in the serum. In a minority of patients, there may be different types of pancreatic NET hormone secretion which may also alter over time (Crona et al. 2016). Occasionally, the synthesis and/or processing of these compounds may be different from that of the eutopically secreted hormone leading to diagnostic uncertainty (Newell-Price 2003). In addition, as the secretion of these hormones is usually aberrantly regulated, the response to endocrine testing is different to that anticipated if eutopically secreted (Kaltsas et al. 2010).

**Diagnostic methods for detecting endocrine PNS**

Suspicion of an endocrine PNS can direct relevant diagnostic investigations accordingly. Non-endocrine tumours associated with endocrine PNS mainly involve the lung, breast, prostate, skin, colon and haematological malignancies. The majority of lung tumours are either small or large cell (SCLC or LCLC), or tumours of squamous origin (Nauck et al. 2007). Squamous cell tumours are usually large and can be detected using conventional cross-sectional imaging (computerised tomography, CT) with a sensitivity and specificity of...
89% and 93%, respectively, in one series (Toyoda et al. 2008); in cases of a suspected lesion without radiological confirmation, 18F-FDG-PET shows 79% sensitivity and 91% specificity (Benjamin et al. 2003). Magnetic resonance imaging (MRI) is increasingly used in the diagnosis for both in situ and invasive forms of breast tumours (Behrendt et al. 2014) with >90% sensitivity but only 72% specificity (Menezes et al. 2014). Multiparametric MRI is widely used for prostate cancer detection with 88% sensitivity and 74% specificity, respectively (De Rooij et al. 2014). Most imaging modalities for malignant skin neoplasms exhibit low sensitivity and specificity, although molecular pathways/targets are currently being explored (Hong et al. 2008). Various imaging methods are employed for the diagnosis of colorectal tumours, yet the ‘gold standard’ remains optical colonoscopy (OC). Other modalities include CT colonoscopy with very high sensitivity (100%), while MRI has 84% sensitivity and 95% specificity when evaluating lesions >1 cm (Kekelidze et al. 2013). In the case of haematological malignancies, CT is the modality of choice (Shankland et al. 2012). PET scanning with 18F-FDG-PET CT is increasingly being used in the management of lymphomas with 80% sensitivity and 90% specificity; however, PET scans are most widely used to assess responsiveness to therapy (Shankland et al. 2012).

Various radiological modalities are utilised for the diagnosis of endocrine tumours. Functional imaging aims at demonstrating the presence of somatostatin receptors (ssr) and uptake mechanisms on their surface (Kwkekeboom et al. 2009). The reported overall sensitivity of somatostatin receptor scintigraphy (SRS) for welldifferentiated (grade 1 and 2) GI-NETs is >80%. The sensitivity of SRS is lower in tumours with a diameter generally <1 cm, 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 ssr expression (Sundin et al. 2012). 68Ga-DOTATATE or 68Ga-DOTATOC is superior to SRS SPECT–CT showing higher sensitivities for lesion detection (>90%), particularly due to better resolution or ssr affinities (Wild et al. 2013). Radioiodinated MIBG, 123I-MIBG, is a guanethidine analogue that shares structural features with noreadrenaline and is used for imaging of phaeochromocytomas, paragangliomas and neuroblastomas (Jacobson et al. 2010). However, 123I-MIBG scintigraphy has lower sensitivity than SRS for GI-NETs (50%) and pancreatic NETs (<10%) (Kaltsas et al. 2001). Fluorine-18-l-3,4-dihydroxyphenylalanine (18F-DOPA) PET/CT showed the highest sensitivity (98%) as compared with SRS and 11C-5-hydroxy-l-tryptophan (11C-5-HTP) PET for the detection of GI-NETs, but not pNETs (Van Essen et al. 2014). 11C-5-HTP is a radiolabelled precursor in the serotonin synthesis; 11C-5-HTP PET showed the highest sensitivity (96%) for the detection of pNETs as compared with CT, SRS or 18F-DOPA PET (Gotthardt et al. 2010). Cholecystokinin2 (CCK2) receptor expression has been demonstrated in NETs with 11In-DOTA-CCK, 99mTc-demogastrix and 111In-DOTAMG11. 68Ga-DOTAtinigastrix radiopharmaceuticals have shown 97% sensitivity for the detection of tumour deposits in patients with medullary thyroid carcinoma (MTC) (Froberg et al. 2009). Another radiopeptide used for targeting the GLP1R is (Lys(40)(Ahx-HYNIC-99mTc/EDDA) NH2)-exendin-4, GLP1R imaging using this compound has been studied in MTCs (Pach et al. 2013).

There is currently a paucity of reliable biomarkers to aid the diagnostic process in cases of non-endocrine neoplasia. This is partially due to the pathobiological diversity of non-endocrine neoplasia and its generally more aggressive biological behaviour (Oberg et al. 2016). In endocrine neoplasia, particularly in NETs, certain markers developed based on specific tumour-secreted compounds can improve chances of tumour detection (Oberg et al. 2016). Besides traditional biomarkers developed for the detection of endocrine malignancy, there is currently a considerable interest in areas such as blood transcript analysis, circulating tumour cells (NetTest) and miRNA measurement, although yet there are significant limitations before application into general clinical practice is likely (Modlin et al. 2016).

Common endocrine PNS secondary to the secretion of peptide hormones

Hypercalcaemia

The hypercalcaemia of malignancy is one of the most common endocrine PNS occurring in up to 10% of all patients with advanced tumours, and conveys a poor prognostic factor as the 30-day mortality can reach 50% (Ralston et al. 1990, Lumachi et al. 2008). Paraneoplastic hypercalcaemia occurs in the absence of metastases or altered parathyroid gland function and can be caused by a variety of humoral substances that exert different effects on calcium homeostasis. Although ectopic parathyroid hormone (PTH) or 1–25-dihydroxy (OH)2 vitamin D3 secretion have been associated with the humoral hypercalcaemia of malignancy (HHM), in the majority of cases (>80%) it results from the secretion of parathyroid
hormone-related protein (PTHrP) (Stewart 2005, Van den Eyden et al. 2007).

Parathyroid hormone is composed of 84 amino acids, whereas PTHrP comprises of 139–173 amino acids; although they exhibit different C-terminal portions they share the first 13 N-terminal amino acids (Stewart 2005, Van den Eyden et al. 2007). PTHrP folds into a configuration that can bind to the PTH receptor, although it can also bind to other receptors, via which it exerts different effects from PTH (Van den Eyden et al. 2007). 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 (Lumachi et al. 2008). It can be produced as four different alternatively-spliced messenger RNA transcripts, and at least two peptide isoforms are known to exist. Hypomethylation of the promoter has been implicated as a mechanism of its aberrant gene expression (Strewler 2000).

PTHrP-related hypercalcaemia occurs most commonly with squamous cell tumours and SCLC (Donovan et al. 2015), but it is also seen with endocrine tumours including GI-NETs (Stewart 2005, Van den Eyden et al. 2007). In two lung squamous cell carcinoma xenograft models of hypercalcaemia, the inhibition of autocrine epidermal growth factor receptor (EGFR) signalling has been shown to reduce plasma PTHrP and total calcium concentrations (Lorch et al. 2007). Amphiregulin stimulation of EGFR resulted in high levels of PTHrP gene expression in squamous cell carcinomas (Gilmore et al. 2009). Furthermore, the reconstitution of the amphiregulin-EGFR signalling system in a squamous cell carcinoma line led to HHM and rapid osteolytic growth in animal models (Gilmore et al. 2009). This is a potential mechanism of non-endocrine neoplasia induced hypercalcaemia. Breast and testicular malignancies, and certain haematological malignancies including multiple myeloma, lymphomas and chronic lymphocytic leukaemia, can cause hypercalcaemia via this mechanism, at least in part (other mechanisms may also be involved) (Shionoiri et al. 2000, Stewart 2005, Kampfenkel et al. 2010). Other malignancies can also be associated with PTHrP-related hypercalcaemia. A recent review identified 29 cases of malignant colorectal tumours causing PTHrP-mediated hypercalcaemia. Most patients were middle-aged men with advanced metastatic cancer and severe hypercalcaemia (62% with Ca >14 mg/dl, 3.5 mmol/L) and were associated with high mortality and a short median survival (Galindo et al. 2016).

PTHrP-related hypercalcaemia is currently considered as the most common mechanism of endocrine tumour-related hypercalcaemia and can be encountered in GI-NETs, phaeochromocytomas and carcinoid tumours (Mantzoros et al. 1997, Abraham et al. 2002, Brzozowska et al. 2009, Kaltas et al. 2010). Pancreatic NETs were initially considered to be a relatively common group of tumours associated with ectopic PTHrP secretion, but a recent single centre study identified this to be a relatively rare event (Kamp et al. 2014).

Rarely, hypercalcaemia may result from ectopic 1,25-dihydroxy(OH)₂ vitamin D secretion, particularly in association with certain haematological malignancies (lymphomas) and NETs, or from ectopic PTH secretion (Stewart 2005, Van den Eyden et al. 2007). Another mechanism of HHM may be mediated by granulocyte colony-stimulating factor (G-CSF), as a long-term exposure to G-CSF results in the stimulation of osteoclastic bone resorption and/or an increase in osteoclast progenitors (Hiraki et al. 2004). The over-secretion of macrophage inflammatory protein 1a (MIP-1a) has also been implicated in a myeloma case simultaneously secreting PTHrP and MIP-1a (Shimizu et al. 2011). Cases of hypercalcaemia attributed to true ectopic PTH secretion are rare. 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 (Kandil et al. 2011). Symptom severity depends not only on the degree of hypercalcaemia (calcium levels >3 mmol/L), but also on the rapidity of onset and the patient’s baseline neurologic and renal function (Stewart 2005). The optimal approach to paraneoplastic hypercalcaemia is the treatment of the underlying tumour. In cases of intractable hypercalcaemia, treatment directed against the elevated calcium levels should be undertaken as per recent guidelines (including bisphophonates and possibly denosumab), while cinacalcet has been shown to be particularly efficacious in cases of PTHrP-related hypercalcaemia (Collins et al. 1998, Takeuchi et al. 2016).

**Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)**

The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is characterised by hypo-osmotic, euvoletic hypernatraemia in the absence of plasma hypotonicity, and it occurs in 1–2% of all patients with malignant tumours (Castillo et al. 2012, Thajudeen et al. 2016). SIADH is most commonly found in SCLC.
although it can also result from LCLC (Raftopoulos 2007, Castillo et al. 2012, Thajudeen et al. 2016). SIADH is also seen in 2–4% of non-SCLC patients, including those suffering from prostate, breast, adrenal cancer and lung carcinoids (Raftopoulos 2007, Castillo et al. 2012, Thajudeen et al. 2016). In SCLC, SIADH has been associated with a higher propensity for central nervous system metastases, poor response to chemotherapy and advanced stage of cancer (Thajudeen et al. 2016). 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 (Selmer et al. 2016); hyponatraemia grade at short-term follow-up was also predictive for long-term survival (Shepshelovich et al. 2015). In primary care patients, all levels of hyponatraemia are associated with increased all-cause mortality, whereas hyponatraemia per se is linked to an increased risk of being diagnosed with any malignancy, particularly pulmonary and head-and-neck malignancies (Selmer et al. 2016).

Inappropriate action of anti-diuretic hormone (ADH, vasopressin), and nearby secreted oxytocin, have been identified in related neoplasms, being also implicated in tumour growth, exhibiting autocrine and paracrine signalling activities (De Lellis & Xia 2003). The relation between SIADH and ectopic ADH production by tumour cells has also been demonstrated in in vitro studies as high concentration of immune-reactive ADH has been found in tumour extracts of patients with SIADH (Thajudeen et al. 2016). Northern blot and S1-nuclease analysis demonstrated the production of ADH mRNA in tumours and tumour cell lines from patients with SCLC and hyponatraemia. Similarly, ADH has also been detected in SCLC tumours by radioimmunoassay and bioassay of anti-diuretic activity. Tissue cultures derived from ADH-producing SCLC demonstrated the presence of ADH in only a fraction of cells. Evidence for the production of ADH by only selected cells is also supported by the finding of persistent SIADH in patients who had a marked decrease in tumour size (Grohe et al. 2015).

The symptoms of SIADH depend on the degree and rapidity of hyponatraemia onset. Serum sodium levels <125 mmol/L, particularly if developing within 48 h, manifest as altered mental status, seizures, coma, respiratory collapse and death (Ellison & Berl 2007). When hyponatraemia develops during a longer time frame, neurologic complications may not occur (Raftopoulos et al. 2007). The optimal therapy for paraneoplastic SIADH is related to the treatment of the underlying tumour, which if successful normalises sodium level in weeks. It has been suggested that in patients with malignancy the use of an ADH receptor antagonist could improve hyponatraemic symptoms even in patients on palliative care. More studies are required to address the potential safety concerns of chronic use, because tolvaptan, a V2-receptor antagonist, is an excellent choice, especially in patients with lung malignancies (Grohe et al. 2015, Thajudeen et al. 2016). It has recently been shown that prompt endocrine input improved time for the correction of hyponatremia and shortened length of hospitalisation, and the widespread provision of endocrine input should be considered (Verbalis et al. 2014, Grant et al. 2015, Tzoulis et al. 2016).

### Cushing's syndrome (CS)

Approximately 10% of Cushing's syndrome (CS) cases are considered to be of paraneoplastic origin with approximately 50% being secondary to lung NETs (bronchial carcinoids, SCLC and rarely LCLC) (Barbosa et al. 2005, Teves et al. 2005, Morandi et al. 2006). Less commonly, paraneoplastic CS (PN-CS) may develop from neuroendocrine cells of the thymus, MTC, pancreas or chromaffin cell tumours (phaeochromocytomas, paragangliomas and neuroblastomas) (Ilias et al. 2005, Isidori et al. 2006). In a recent study performed by Kamp and coworkers looking at a large cohort of patients with thoracic and GEP-NETs, the reported prevalence of PN-CS was 3.2% (Kamp et al. 2016).

It can also rarely arise from NE cells originating from the ovary or prostate (Nimalasena et al. 2008). Paraneoplastic CS occurs secondary to tumour secretion of adrenocorticotrophic hormone (ACTH) or very rarely of corticotrophin-releasing hormone (CRH) (Newell-Price et al. 1998, Newell-Price et al. 2006). The ectopic ACTH syndrome is caused by abnormal expression of the POMC gene product arising from non-pituitary tumours in response to ectopic activation of the pituitary-specific promoter of this gene. Methylation of the CpG islands in the promoter region is associated with silencing of some genes. 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 (Ye et al. 2005). 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 (Newell-Price 2003).

Endocrine and neuroendocrine tumours producing PN-CS are in the majority of low malignant potential although this may change during the course of the disease (Ilias et al. 2005, Isidori et al. 2006, Li et al. 2016). Well differential lung NETs (typical and atypical carcinoids) account for the majority of PN-CS, approximately 36–46%, producing a clinical and biochemical syndrome resembling pituitary dependent CS (Li et al. 2016, Zhang & Zhao 2016). Symptoms and biochemical manifestations typically evolve gradually and usually do not produce a severe CS phenotype (Li et al. 2016). Although a variety of invasive and non-invasive endocrine and imaging studies may be utilised, a number of these tumours may still elude localisation or become apparent later during the course of the disease (Hofland & Lamberts 2001). In such cases medical treatment of hypercortisolaeemia and regular imaging studies to identify such lesions is usually advocated (Nieman et al. 2015). Paraneoplastic CS syndrome due to ACTH secretion from MTC appears to be relatively rare as it was only detected in 10/1640 patients with MTCs (0.6%) (Barbosa et al. 2005). Phaeochromocytomas secreting ACTH are considered to be even rarer, accounting for approximately 5.2% of all cases of ectopic ACTH related CS (Ballav et al. 2012). Pancreatic NETs associated with PN-CS account for up to 10% of ectopic CS. In a recent study of 10 pNETs causing PN-CS, the mean age at diagnosis was 42 years, whereas the 5 and 10 year overall survival rate was 35% and 16.2%, respectively (Maragliano et al. 2015). Thymic NETs associated with PN-CS are also relatively rare and are usually associated with a worse outcome, but ectopic ACTH is a fairly common manifestation of thymic carcinoids and may occur in association with MEN-1 (Jia et al. 2017). In a study of 12 patients the median age at presentation was 21 years, median tumour diameter 5 cm, while urinary free cortisol levels were found to be grossly elevated (Neary et al. 2012). Six recurrent patients developed metastatic disease and died 57 months following initial thymectomy (Neary et al. 2012). Figure 1 illustrates a thymic carcinoid tumour which secreted ACTH intermittently to cause periodic Cushing's syndrome (Trott et al. 2016).

Paraneoplastic CS from NETs has occasionally been attributed to CRH secretion such as carcinoids, MTCs and chromaffin cell tumours (Ilias et al. 2005, Isidori et al. 2006). In such cases, endocrine testing may be difficult to interpret as there is interplay between the findings of ectopic and eutopic production of these compounds, although usually there is a co-secretion of both ACTH and CRH (Howlett et al. 1986, Oldfield et al. 1991, Chrysoulidou et al. 2008).

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 (Ilias et al. 2005, Isidori et al. 2006, Kaltetas et al. 2010). In contrast to patients with PN-CS derived from NETs, patients with SCLC do not generally exhibit the classical symptoms of gradually evolving endogenous hypercortisolaeemia with the exception of being exposed to high levels of cortisol (Bollanti et al. 2001, Ilias et al. 2005, Isidori et al. 2006). The symptoms/signs of the underlying malignancy along with weight loss, electrolyte and metabolic abnormalities are commonly encountered (Bollanti et al. 2001, Ilias et al. 2005, Isidori et al. 2006). The diagnosis is usually suspected on the basis of the rapidity of symptom development, relevant history of excessive smoking and radiological findings (Rueda-Camino et al. 2016). The severity of PN-CS can occasionally be so excessive that it may lead to cardiorespiratory failure (von Stempel et al. 2013). The impact of PN-CS in SCLC patients has been evaluated in a recent study (Nagy-Mignotte et al. 2014). Among 383 patients with SCLC, 23 had PN-CS, 56 other PNS (OtherPNS) and 304 had no PNS (NoPNS). 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% vs 74.1% vs 71.1%) and poorer sensitivity to first-line treatment (19% vs 38.9% vs 48.6%), respectively. On relapse, the PN-CS group had no objective response to second-line treatment vs 25%
and 42.8% in OtherPNS and NoPNS groups, respectively (Nagy-Mignotte et al. 2014). The median survival of PN-CS patients was 6.6 months vs 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) (Nagy-Mignotte et al. 2014).

Small cell carcinoma (SCC) of the prostate is an uncommon condition but there are a very few cases in which presenting symptoms are consistent with CS (Rueda-Camino et al. 2016). It may be suspected when laboratory features appear in patients diagnosed with prostatic adenocarcinoma with metastases that becomes resistant to specific therapy; prostatic-specific antigen levels are usually normal. The prognosis is very poor as 2- and 5-year survival rates are 27.5 and 14.3%, respectively (Rueda-Camino et al. 2016). Ectopic ACTH secretion associated with CS can also be rarely due to pancreatic acinar cell carcinoma (ACC) and pancreatoblastoma, rare tumour types with morphologic features sometimes overlapping those of pNETs (Maragliano et al. 2015).

Several studies have attempted to provide clinical, biochemical and radiological features aiming at distinguishing the origin of PN-CS in respect to the malignant potential of the tumour (Table 3).

PN-CS treatment focuses on the management of the severe metabolic disruptions followed by rapid resolution of the hypercortisolaemia, and subsequent confirmation of the cause. Emergency lowering of the elevated serum cortisol when the syndrome is severe is most rapidly achieved with oral metyrapone and/or ketoconazole; if parenteral therapy is required then intravenous etomidate is rapidly effective in almost all cases (Preda et al. 2012), but all measures require careful supervision. If medical treatments fail, bilateral adrenalectomy should be performed in the shortest possible time span to prevent the debilitating complications of uncontrolled hypercortisolaemia (Nieman et al. 2015).

### Table 3  Endocrine and non-endocrine tumours causing paraneoplastic syndromes.

<table>
<thead>
<tr>
<th>Paraneoplastic syndrome</th>
<th>Tumour types</th>
</tr>
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<tbody>
<tr>
<td>Common</td>
<td>Squamous cell (head and neck, lung, skin), breast, genitourinary (ovary, testis), lymphomas, renal, multiple myeloma, chronic lymphocytic leukaemia, lung (SCLC), colorectal, GI-NETS</td>
</tr>
<tr>
<td>Humoral hypercalcaemia of malignancy (HHM)</td>
<td>Lung (squamous, SCLC, LCLC, bronchial carcinoids), prostate, breast, adrenal, GI</td>
</tr>
<tr>
<td>Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)</td>
<td>Lung (SCLC, bronchial carcinoids, LCLC), thymus, MTC, pNET, pheochromocytomas, pargangiomas, neuroblastomas</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Mesenchymal tumours (sarcomas, GIST), renal, ovarian, NETs</td>
</tr>
<tr>
<td>Less common</td>
<td>Lung (SCLC, bronchial carcinoids), GCT (seminomas, teratomas, choriocarcinomas, yolk sac), pNETs</td>
</tr>
<tr>
<td>Non-islet cell tumour hypoglycaemia (NICTH)</td>
<td>pNETs, lung (bronchial carcinoids), choriostomas, hamartomas, gliomas, gangliocytomas</td>
</tr>
<tr>
<td>Gynaecomastia/virilisation (β-hCG)</td>
<td>Lung (SCLC, bronchial carcinoids), paragangiomas, renal, DSRCT</td>
</tr>
<tr>
<td>Rare</td>
<td>Lung (SCLC), mesenchymal tumours</td>
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<tr>
<td>Acromegaly</td>
<td>Ectopic pituitary adenomas, struma ovarii</td>
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<td>Hypertension</td>
<td>Lung (SCLC), MTC, pheochromocytoma, renal</td>
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<td>Ovarian hyperstimulation syndrome/PCOS like</td>
<td>Mesenchymal tumours, prostate, colon</td>
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<td>Hyperprolactinaemia</td>
<td>Glomus tumours (skull base)</td>
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<td>Hyperthyroidism</td>
<td>Pheochromocytomas, mesenchymal tumours, angiomatoid fibrous histiocytoma</td>
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<td>Secretory diarrhoea</td>
<td>Base</td>
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<td>Tumour induced osteomalacia (TIO)</td>
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<td>Ileus</td>
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<td>Acute inflammatory reaction/pyrexia</td>
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β-hCG, beta-human chorionic gonadotrophin; DSRCT, desmoplastic round cell tumours; GI-NETS, gastrointestinal neuroendocrine tumours; GIST, gastrointestinal stromal tumours; LCLC, large cell lung carcinoma; MTC, myeloid thyroid carcinoma; PCOS, polycystic ovary syndrome; pNETs, pancreatic neuroendocrine tumours; SCLC, small cell lung carcinoma.
glucose utilisation by different mechanisms such as insulin-like growth factor 2 (IGF2) precursors, IGF1 and glucagon-like peptide-1 (Kaltsas et al. 2010, Iglesias & Diez 2014). Tumour autoimmune hypoglycaemia may also occur secondary to insulin receptor auto-antibody production, whereas excessive tumour burden with glucose consumption, massive tumour liver infiltration, and pituitary or adrenal gland destruction by the tumour are the other mechanisms in cases of large and aggressive neoplasias (Iglesias & Diez 2014).

Non-islet cell tumour hypoglycaemia (NICTH) presents as recurrent or constant hypoglycaemic episodes and mostly affects elderly patients with advanced tumours (Teale & Wark 2004, Dimitriadis et al. 2015). Occasionally, these hypoglycaemic episodes can predate the diagnosis of the underlying tumour (Nayar et al. 2006, Kim et al. 2016). The majority of cases of NICTH are usually caused by tumour cell production of IGF2 (Iglesias & Diez 2014). NICTH is characterised by low serum insulin and C-peptide levels, low growth hormone (GH) and IGF1 levels, normal or elevated IGF2 levels and an elevated IGF2:IGF1 ratio (Teale & Wark 2004, Nayar et al. 2006, Iglesias & Diez 2014). In some cases of NICTH, expression of 'big' IGF2 has been reported and rarely there is expression of pro-IGF2 (Beckers et al. 2003, Hamberg et al. 2006). High concentrations of pre-pro-IGF2 levels that are not properly glycosylated result in the high molecular weight ‘big’ IGF2 that has a significantly higher affinity to the insulin receptor, and a lower affinity to its binding protein (IGFBP3), leading to increased bioavailability, enhanced peripheral glucose consumption and suppressed hepatic glucose production (de Groot et al. 2007, Rikhof et al. 2009). The majority of tumours associated with NICTH are mesenchymal and epithelial tumours although a number of NETs have also been described (de Groot et al. 2007, Kaltsas et al. 2010). In a recent review, 32 cases of IGF2 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 (Otake et al. 2015). 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 IGF2 not responding to everolimus was recently reported by Korevaar and coworkers (Korevaar et al. 2014). It appears that either IGF2 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 IGF1R and insulin receptor A or B may form receptor hybrids when co-expressed on the same cell (Korevaar et al. 2014).

A case of ectopic insulin secretion by a renal cell carcinoma with positive 68Ga-DOTANOC imaging and ex-vivo immunoreactivity for insulin has recently been reported (Ramkumar et al. 2014), along with an ovarian tumour of mixed neuroendocrine and yolk origin secreting insulin, leading to paraneoplastic hypoglycaemia (Battocchio et al. 2015).

**Acromegaly**

Acromegaly unrelated to a pituitary GH-secreting adenoma is very rare, accounting for less than 1% of cases (Melmed et al. 2006). Since the discovery of growth hormone-releasing hormone (GHRH) 30 years ago, it became apparent that the majority of these cases are GHRH-related as this peptide can be synthesised and expressed in multiple extrapituitary tissues (Christofides et al. 1984, Melmed et al. 2006). In a recent review, only 74 published cases were identified and except for a recent French series of 21 cases most were case reports (Garby et al. 2012). Tumours secreting GHRH are mainly NETs, usually well-differentiated and of pancreatic or bronchial origin accounting for approximately 2/3 of cases (Fainstein et al. 2007, Butler et al. 2012, Lock et al. 2014). The clinical presentation is variable with features similar to those caused from a somatotroph adenoma. These tumours are usually large and easy to localise whereas the pituitary imaging may be normal or enlarged and difficult to interpret, especially in multiple endocrine neoplasia type-1 (MEN1) cases. Plasma GHRH measurement has an excellent specificity for the diagnosis, using a threshold of 250–300ng/L, and is a good tool for the follow-up of patients after treatment. These tumours have a good overall prognosis although approximately 50% develop metastases (Borson-Chazot et al. 2012). Single cases of NETs causing acromegaly have been described from the duodenum (Colak Ozbey et al. 2009), liver (Furrer et al. 2001) and pancreatic tumours in the context of MEN1 (Biermasz et al. 2007, Weiss et al. 2011, Sala et al. 2013). Hypothalamic tumours, including hamartomas, choristomas, gliomas and gangliocytomas, may also produce excessive GHRH resulting in acromegaly (Di Lorgi et al. 2007). Ectopic secretion of GH has only been described in single cases (Melmed et al. 2006, Fainstein et al. 2007) and represents approximately 0.1%
of paraneoplastic acromegaly cases (Melmed et al. 2006, Fainstein et al. 2007).

Less common endocrine PNS secondary to the secretion of peptide hormones

**Ectopic renin secretion** Cases of extra-renal renin-producing tumours are particularly rare, mostly related to NETs (paragangliomas and carcinoids) and SCLC leading to a hypertensive PNS (Dayal et al. 1986). Other extremely rare cases of renin-secreting tumours including desmoplastic round cell tumours (DSRCT) secreting ectopic renin (Lee et al. 2014). Cases of renin secretion from renal or pulmonary carcinomas have also been described (Ganguly et al. 1973). 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 chemotherapy regimes. Adjuvant use of various anti-hypertensives, spironolactone or rarely aliskiren has proven to be helpful in offering temporary symptom relief (Rosei et al. 2015).

**Ectopic β-human chorionic gonadotrophin (bhCG production)** Gynaecoma is a relatively rare PNS associated with tumour-secreted bhCG. There are several reports of paraneoplastic gynaecomatia secondary to thoracic (mainly SCLCs, carcinoids and extragonadal germ cell tumours) clinically associated with gynaecoma in men, menstrual irregularity and virilisation in women, and precocious puberty in children (Braunstein et al. 1972, DeLellis & Xia 2003, Yaturu et al. 2003, Mehta et al. 2008, Dimitriadis et al. 2017). Rarely, secretion of bhCG results from clear cell renal tumours (Mohammed et al. 2008) or liver carcinomas (Teniola & Ogunleye 1994). A bhCG-like protein is also found in a variety of normal tissue, and there is evidence to suggest that the ahCG subunit may exert a paracrine effect on the growth of tumour cells (Rivera et al. 1989); bhCG may also act as a growth factor in SCLCs (Szturmowicz et al. 1995). Treatment is tumour resection or multi-agent chemotherapy in cases of chemo-sensitive malignancies such as SCLC.

**Ectopic gonadotrophin production** A handful of cases of ectopic gonadotrophin-secreting tumours leading to PNS are reported in the literature. In cases of the ectopic secretion of follicle stimulating hormone (FSH), patients may present with ovarian hyperstimulation syndrome (Roberts et al. 2005, Burgos et al. 2009, Miras et al. 2015). Ectopic secretion of luteinising hormone (LH) has also been described presenting with phenotypic characteristics resembling the polycystic ovary syndrome (PCOS, Brignardello et al. 2004, Piaditis et al. 2005). Definitive treatment for these rare tumour cases remains the resection of the primary site.

**Other ectopic pituitary hormone secretion** Ectopic secretion of prolactin secondary to a SCLC has been reported (Turkington 1971). Another case of hyperprolactinaemia secondary to a low-grade malignant mesenchymal tumour of the uterus with positive SRS has also been described (Simsir et al. 2012). Following successful removal of the mass, the hyperprolactinaemia which was previously refractory to dopamine agonist treatment was resolved, but immunohistochemistry for prolactin was negative (Simsir et al. 2012). Anecdotal cases of ectopic TSH secretion have been mentioned in the literature; ectopic TSH-secreting pituitary adenomas have occasionally been described (Bollanti et al. 2001, Pasquini et al. 2003).

**Ectopic gut hormone secretion** Paraneoplastic syndromes associated with ectopic secretion of gut peptides are very rare. Cases of vasoactive intestinal polypeptide (VIP) secretion causing typical watery diarrhoea has been described secondary to SCLC, MTC, phaeochromocytoma and NETs arising from the kidney (Said & Falona 1975, Tischler et al. 1984). Glucagon-like peptides (GLP) 1 and 2 are hormones derived from the post-translational processing of pro-glucagon in the intestinal L cells that influence intestinal motility and small bowel growth, respectively. A case of a GLP1 and somatostatin-secreting NET has been reported presenting with reactive hypoglycaemia and hyperglycaemia subsequently cured by surgery (Todd et al. 2003). Another case of a well-differentiated NET of unknown primary origin presenting with diffuse metastases, constipation and nocturnal itching with positive immunostaining for GLP1, GLP2 and polypeptide YY (PYY) has been described. Jejunal biopsy demonstrated marked intestinal mucosal hypertrophy. High-performance liquid chromatography (HPLC) analysis combined with radioimmunoassay (RIA) of tumour and serum extracts revealed that the tumour was secreting and releasing GLP1 and GLP2, as well as PYY (Byrne et al. 2001). Ectopic secretion of ghrelin, in the serum of a patient with a pNET has been reported, as well as a carcinoid of the stomach.

Other rare peptide hormones Ectopic calcitonin over-secretion is rare. A case of a SCLC presenting with dual PNS including over-secretion of ACTH and calcitonin has been described (Coners et al. 2011). Presenting symptoms included metabolic alkalosis with hypokalaemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, hyperglycaemia and profound diarrhoea (Coners et al. 2011). There are several other cases of ectopic calcitonin secretion by SCLC, LCLC or lung carcinoids (Kelley et al. 1994, Machens et al. 2000, Cvijovic et al. 2013).

Tumour-induced osteomalacia (TIO) is a rare PNS manifested with bone and muscular pains, bone fractures, and sometimes loss of height and weight (Dadoniene et al. 2016). 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 (Miyauchi et al. 1988). Fibroblast growth factor FGF23 is secreted by the bones and was first identified as the phosphaturic agent when mutations in FGF23 gene were linked to autosomal dominant hypophosphataemic rickets (ADHR) (White et al. 2001). In cases of TIO, FGF23 (FGF23/Klotho system) secretion is much higher leading to dysregulation of the FGF23 degradation pathway (Hannan et al. 2008). Tumours usually bearing the ability to over-secrete FGF23 are generally of mesenchymal origin, but there are cases of an adenocarcinoma of the colon and prostate (Ramon et al. 2011, Mak et al. 2012, Leaf et al. 2013). FGF23 measurements combined with 18FDG PET/CT SCAN can be a decisive tool in cases of TIO, and is likely going to be of considerable importance for facilitating early diagnosis and follow-up (Dupond et al. 2005). Current management of TIO involves tumour resection. However, the development of a humanised anti-FGF23 antibody for adult patients with X-linked hypophosphataemic rickets (XLHR) may be useful for patients with TIO with similar pathogenesis to that of XLHR (Kinoshita & Fukimoto 2014).

Hypertrophic osteoarthropathy (HOA) is a syndrome characterised by proliferative changes in the skin and skeleton. In addition, it may also comprise of proliferative periostitis of the long bones, oligo- or polysynovitis and digital clubbing (Dubrey et al. 2016). There are two types of hypertrophic osteoarthropathy: primary and secondary. Only 3–5% of patients have primary HOA while the remaining 95–97% have secondary HOA, commonly associated with many disease conditions of the cardiovascular system and hepatobiliary gastrointestinal system as well as in malignancies, including neuroendocrine carcinomas of the oesophagus and lungs (El Bakkal et al. 2011, Saif & Vethody et al. 2016). Current evidence favours a pathology based on inadequate uptake or metabolism of prostaglandin E2.

Ectopic oxytocin secretion is a very rare PNS but has been reported in cases of SCLC (Shigetomi et al. 1980, Wilson & Ngee 1980). A case of an SCLC tumour cell line from a patient with PN hyponatraemia was shown to ectopically produce, process and secrete ANP in the same immunoreactive form as the biologically active molecule. It apparently contained an enzyme that could cleave precursors at the same amino acid sequences needed to produce ANP-(S99-Y126) from pro-ANP (Johnson et al. 1997). The recent demonstration of human placental lactogen (hPL) in serum samples of 12 patients with testicular malignancy and highly elevated levels of holo-hCG (mean: 42.490 ng/mL) suggest an auto/paracrine function of this molecule (Madersbacher et al. 1998). Cases of SCLCs and phaeochromocytoma have also been reported secreting hPL (Kaltsas et al. 2010).

There is evidence that glomus tumours of the skull base (head-and-neck paragangliomas) may secrete neuropeptides, such as cholecystokinin, in addition to catecholamines (Jackson et al. 1989). High circulating levels of cholecystokinin associated with these tumours may be responsible for the unexplained phenomenon of prolonged post-operative ileus (Jackson et al. 1989).

Endocrine paraneoplastic syndromes secondary to the secretion of non-peptide agents Cytokines In recent years, increasing evidence has been adduced that phaeochromocytomas are capable of secreting cytokines, mainly interleukin-1 (IL1) (Bornstein et al. 1996, Liu et al. 2000), IL6 (Shimizu et al. 2001), tumour necrosis factor-α (TNFa) and interferon-γ (IFNg) (Tirone et al. 1989). In such cases marked inflammatory reactions and pyrexia were improved on either non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, but subsided after adrenalectomy (Minetto et al. 2003). Non-endocrine tumours producing cytokines are usually of mesenchymal origin; a recent case
reported an angiomatoid fibrous histiocytoma presenting with severe inflammatory symptoms, being immunohistopathologically positive for IL-6 and Tyr705-phosphorylation of signal transducer and activator of transcription 3 (STAT3) (Akiyama et al. 2015). The EWSR1-CREB1 fusion gene detected in the tumour led to continuous activation of CREB1 and IL6 production because the promoter region of IL6 has a CREB binding site (Akiyama et al. 2015).

Steroid and other endocrine PNS related compounds A number of mesenchymal cells can differentiate into steroidogenic cells following ectopic expression of nuclear factor (NR) SA subfamily proteins, steroidogenic factor-1 and liver receptor homolog 1 (Yazawa et al. 2016). 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 (Yazawa et al. 2016).

Paraneoplastic hyperaldosteronism has been described in a patient with ovarian cancer and also in cases of Non-Hodgkin’s lymphoma (NHL) (Todesco et al. 1975, Mulatero et al. 2001). It has been suggested that paraneoplastic hyperaldosteronism could be secondary to the expression of the CYP11B2 gene (Mulatero et al. 2001). In a patient with NHL and unexplained hypertension, RNA extraction from a lymph node demonstrated increased CYP11B2 mRNA expression, confirming that hyperaldosteronism was paraneoplastic (Mulatero et al. 2001). Struma ovarii is a rare subtype of ovarian cancer representing <1% of all ovarian malignancies (Lara et al. 2016). 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 (Lara et al. 2016). Gestational trophoblastic diseases comprise hydatidiform moles, invasive moles, choriocarcinomas and placental site trophoblastic tumours. Hydatidiform moles and choriocarcinomas that secrete high amounts of hCG can cause hyperthyroidism (Kopp 2010).

Conclusions

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. These syndromes affect the presentation, clinical course and treatment of such patients. As a result of recent diagnostic and therapeutic advances, many PNS are currently well defined, and some effective treatment options are evolving. The ability to recognise and treat PNS may have a substantial effect on clinical outcomes, ranging from earlier cancer diagnosis, to improved quality of life, to increased delivery of tumour-directed therapy. Furthermore, on-going research into these disorders may shed light on mechanisms of tumour development, maintenance and proliferation. However, as the exact prevalence of PNS is still a matter of debate, registration of these syndromes seems imperative to help identify their exact aetiology and their effect on the disease process.

Declaration of interest

G K D, A A, M O W and H S R declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review. G K and A G have received advisory board and lecture fees from pharmaceutical companies.

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