Endocrine abnormality in paraneoplastic syndrome

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Introduction

Endocrine abnormalities in paraneoplastic syndrome (PNS) are phenomena denoted by the ability of neoplastic cells to create endocrinopathy. These are unrelated to direct local or metastatic tumour...
effects and are instead related to the acquired production and release of bioactive substances namely hormones, functionally active peptides and cytokines. Release of such substances can be mediated by neoplastic cells with or without endocrine differentiation and notably diagnosis of endocrine abnormalities can sometimes pre-date cancer diagnosis. These syndromes are termed paraneoplastic because the secretory components responsible for their development are not derived from the anticipated organ or tissue of origin. 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 neoplasm (see Fig. 1).

Reports of endocrine syndromes in non-endocrine carcinomas date back as early as the 1920s [1]. The definitive management of paraneoplastic endocrine syndromes remains effective surgical and/or medical anti-tumour interventions alongside interim medical interventions to manage the immediate direct effects/symptoms of the endocrine disorder at hand.

Pathophysiology

The precise mechanisms underlying atypical secretion of bioactive substances from tumour cells remain unclear. Various hypotheses exist in this area. Different non-endocrine tissues exhibit hormone secretion for autocrine control which can be increased by neoplasia. Additionally following the stem cell theory all cells carry the same genetic information with only a portion of these being expressed during the life cycle. However, under certain conditions such as cellular proliferation in neoplasia it is felt that genetic and epigenetic changes can occur which activate genes regulating hormone synthesis [2].

Symptoms are produced by the secretion of bioactive substances from tumour cells directly into the circulation (although they may also exert paracrine and autocrine effects). At this stage hormone levels are expectedly elevated in the serum and due to aberrant regulation, the response to endocrine testing often deviates from that seen in eutopic hormone production [3].

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**Fig. 1.** Organ specific effects of pathophysiological excess IGF-2 secretion from tumour cells.
Neuroendocrine neoplasms (NENs) can also be associated with paraneoplastic endocrine abnormalities. These neoplasms form a heterogeneous group of mainly well differentiated tumours with a favourable prognosis. A large number of such have been reported, displaying the signs and symptoms similar to those when the secretory bioactive product is produced from the expected site of origin [4].

Diagnosis

For the diagnosis of a paraneoplastic endocrine syndrome there should be clinical or biochemical evidence of endocrine abnormality on the background of neoplastic disease and in the absence of a native endocrine disorder.

Diagnostic criteria have been proposed which include detection of elevated hormone concentrations in combination with normal or suppressed endogenous hormone production. Also, demonstration of increased hormone gradients across the tumour and biochemical/clinical resolution of the syndrome following tumour treatment (e.g. surgery, radiotherapy, chemotherapy) provide further evidence for ectopic hormone production. Detection of relevant tumour mRNA for the specified hormone production is additionally useful information [1]. Diagnostic criteria are shown in Table 1.

Typically, endocrine abnormalities in PNS originate from the production of bioactive substances from the lungs, gastrointestinal tract, pancreas, thyroid, adrenal medulla, skin, prostate or breast. Distinguishing ectopic hormone production from an initially anticipated eutopic endocrine tumour can represent a diagnostic challenge. Endocrine syndromes related to non-endocrine tumours mostly occur in highly malignant tumours; however importantly they do not always correlate with tumour stage, malignant potential or prognosis [2].

Imaging studies provide a cornerstone for primary tumour diagnosis and/or metastases at a time where an associated endocrine abnormality may or may not be known. Computed tomography (CT) scanning remains an effective diagnostic tool. A large prospective cohort study showed sensitivity and specificity rates in the detection of lung cancer of 88.9% and 92.6% respectively for low dose CT [5]. Additionally, CT colonography in meta-analysis has shown sensitivity up to 96.1% in the detection of colorectal cancer [6]. MRI has notable detection rates for tumours of the brain, spinal cord, bones, prostate and pelvic organs. 18F-FDG PET/CT is common practise in the characterization and management of lymphoma combining functional and morphological information. In a case series 97–100% of patients with Hodgkin’s lymphoma and diffuse large B cell lymphoma showed hypermetabolic features on 18F-FDG PET imaging [7]; it is also a widely adopted imaging technique to assess tumour responsiveness to therapy.

Concomitant neuroendocrine tumours (NETs) can be diagnosed by elevation of the universal serum marker Chromogranin A in combination with typical imaging findings. Octreotide scintigraphy is an important imaging tool which can help localise tumours in patients with NETs based on the expression of somatostatin receptors (SSTRs) by tumour cells achieving sensitivities between 67 and 100% depending on tumour type [8]. 68Ga-DOTATATE PET is a newer nuclear medicine imaging technique showing higher sensitivities for lesion detection assisted by increased SSTR affinity and better resolution. 123I-MIBG scanning has a lower sensitivity than somatostatin scintigraphy for detecting GI-

| Table 1 |
| Criteria for defining ectopic hormonal (paraneoplastic) syndromes. |
| Endocrine or metabolic abnormality in a patient with a neoplasm |
| Symptom remission after effective treatment |
| Endocrine syndrome recurrence with disease relapse |
| Abnormally regulated elevated hormone concentration |
| Significant gradient between hormone concentration in the venous effluent from the tumour and arterial hormone levels |
| Tumour samples exhibit bio- and/or immunoreactive hormone |
| Relevant hormone mRNA can be identified in tumour tissue |
| Synthesis and secretion of relevant hormone by tumour cells in vitro |
NETs and pancreatic NETs but this modality uses an analogue sharing a similar structure to noradrenaline making it an effective modality for detecting phaeochromocytomas, paragangliomas and neuroblastomas [3].

Common endocrine paraneoplastic syndromes secondary to peptide hormones

Hypercalcaemia of malignancy

Definition

Hypercalcaemia of malignancy is the most common paraneoplastic endocrine syndrome occurring in up to 30% of persons with malignancy at some point over the course of their disease [9,10]. It denotes typically markedly elevated serum calcium levels on the background on known or suspected malignancy. It is a poor prognostic marker with a 30-day mortality rate reaching 50% [3]. However recent analyses of 4874 patients revealed lower in-patient mortality rate of 6.8% [11]. In early carcinoma diagnosis, the incidence of associated hypercalcaemia is low (1–5%) but this increases in advanced stage disease; being four times more common in stage IV carcinoma [9,12].

Pathogenesis

Associated hypercalcaemia can be classified into four categories as listed in Table 2. Most commonly in 80% of cases the underlying cause lies in the secretion of parathyroid hormone (PTH)-related peptide (PTHrP) by malignant tumours; this condition is also known as humoral hypercalcaemia of malignancy (HHM). The additional categories for consideration are local osteolytic hypercalcaemia, 1,25-dihydroxyvitamin D (1,25(OH)₂Vit-D) secreting tumours and rarely ectopic secretion of PTH (ectopic hyperparathyroidism) [10].

PTHrP is structurally similar to traditional PTH. PTH is composed of 84 amino acids whereas PTHrP consists of 139–173 amino acids exhibiting different C-terminal portions but sharing the same first 13 N-terminal amino acids [3]. 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. In a similar fashion PTHrP will bind to receptors in the kidneys and bones enhancing renal tubular reabsorption of calcium while simultaneously increasing urinary phosphorus excretion in addition to increased bone calcium resorption [13]. Notably PTHrP is present in a wide variety of cells and tissues with various other roles including the relaxation of vessels and smooth muscle cells, and the regulation of development [14]. However, it is not known to increase 1α-hydroxylase activity therefore 1,25(OH)₂Vit-D levels do not increase in PTHrP related hypercalcaemia in malignancy. Commonly associated malignancies are squamous cell carcinomas including those of head & neck, oesophageal, cervical, lung and colon cancers in addition to renal cell, bladder, breast, endometrial and ovarian cancers; it is rarely seen in pancreatic neuroendocrine tumours [9]. The PTHrP gene is located on the short arm of chromosome 12 and hypomethylation has been suggested as the mechanism of expression in cases of PTHrP related hypercalcaemia [1]. The ras-MapK pathway likely represents the common mechanism by which various stimuli activate PTHrP gene expression: these stimuli include growth factors (namely tumour related growth factor TGF-β), angiotensin, cytokines and phorbol esters [15].

Local osteolytic hypercalcaemia tends to account for 20% of cases of malignancy related hypercalcaemia where local osteolytic metastases cause increased released of calcium from the bones. Local tumour cytokine release stimulates increased PTHrP production and subsequent RANKL/RANK

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence (%)</th>
<th>Bone Metastasis</th>
<th>Causal Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral Hypercalcaemia</td>
<td>80</td>
<td>Uncommon and minimal</td>
<td>PTHrP</td>
</tr>
<tr>
<td>Osteolytic Hypercalcaemia</td>
<td>20</td>
<td>Common and extensive</td>
<td>Cytokines, chemokines, PTHrP</td>
</tr>
<tr>
<td>Ectopic 1,25(OH)₂Vit-D secretion</td>
<td>&lt;1</td>
<td>Variable</td>
<td>1,25(OH)₂Vit-D</td>
</tr>
<tr>
<td>Ectopic PTH secretion</td>
<td>&lt;1</td>
<td>Variable</td>
<td>PTH</td>
</tr>
</tbody>
</table>

Table 2

Hypercalcaemia mechanisms and characteristics.
interaction causing amplified osteoclastic activity and bone resorption. Implicated cytokines include interleukin-1 (IL-1), IL-3, IL-6, TNFα, TGFα, lymphotoxin and prostaglandins E series [12]. Metastatic breast cancer, multiple myeloma and lymphomas commonly present via this mechanism [16]. Macrophage inflammatory protein 1α (MIP1α) has also been reported to play an important role in hypercalcaemia associated with multiple myeloma. MIP1α has been found to be elevated in the bone marrow of patients with active myeloma and is known to stimulate osteoclastic formation in human bone marrow cells [9].

Only 1% of cases are related to ectopic production of active 1,25-dihydroxyvitamin D (1,25(OH)2Vit-D) from tumour cells. It is particularly seen in association with haematological malignancies and NETs [3]. Additionally, it is seen in various non-malignant granulomatous disorders such as sarcoidosis and tuberculosis. The underlying mechanism is due to pathological cells and adjacent macrophages acquiring the ability to express 1α-hydroxylase leading to the conversion of endogenous 25-hydroxyvitamin D into the active metabolite 1,25-dihydroxyvitamin D; this metabolite binds to gut receptors causing increased intestinal calcium absorption and hypercalcaemia [12].

Hypercalcaemia in malignancy secondary to true ectopic PTH secretion is extremely rare. Literature review has revealed approximately 30 cases to date involving neoplasms of the head & neck, thorax, GI-pelvis and NETs [3]. In a similar fashion to primary hyperparathyroidism, hypercalcaemia is caused as consequence of PTH receptor activation leading to increased calcium bone resorption, increased renal reabsorption and increased generation active 1,25(OH)2Vit-D.

**Historical perspectives**

The first descriptions of hypercalcaemia of malignancy were described in 1924. In 1936 a case of hypercalcaemia was diagnosed of obscure cause on the background of bronchogenic carcinoma without metastases and with normal parathyroids. In 1941 American endocrinologist Fuller Albright described a case of a 51 year old male with a right ilium lytic lesion metastatic deposit from renal cell carcinoma. There was associated hypercalcaemia and hypophosphatemia, and after irradiation of single bone metastasis the hypercalcaemia resolved; this led early postulations of an underlying disorder of a secretion of a PTH-like related substance. The PTHrP sequence was eventually obtained in 1987 from cultured human squamous cell line in a patient with hypercalcaemia and sensitive bioassays are now widely available to identify this [17].

**Symptoms and diagnosis**

The clinical symptoms of hypercalcaemia include nausea, polyuria, polydipsia, confusion, fatigue, bone pain, loss of appetite and constipation; which often correlate with the severity of the hypercalcaemia and can have a rapid onset. Typical laboratory findings include an elevated calcium level, suppressed or low normal PTH level and an elevated PTHrP level. HHM may co-present with primary hyperparathyroidism which may further complicate diagnosis and management of hypercalcaemia. The diagnosis of humoral hypercalcaemia is often clear on clinical grounds; therefore, the routine testing of PTHrP levels is not required [10]. In the absence of an ionized calcium level a total calcium level should be corrected for albumin concentration [16]. It is important to consider other factors that may be causing or contributing to hypercalcaemia including the administration of thiazide diuretics, lithium, oral calcium, vitamin D supplements and granulomatous disorders.

**Treatment**

Treatment should be primarily directed towards the underlying tumour. However, it is important to simultaneously employ adjunctive therapies to help to manage moderate to severe hypercalcaemia. Therapies should be targeted at the degree of hypercalcaemia, symptoms and the underlying cause. European and Australian guidelines exist for management including the use of intravenous fluids initially and additional key therapies including bisphosphonates, denosumab, glucocorticoids, calcimimetics and calcitonin [18,19].

This cohort of patients are commonly volume depleted leading to renal insufficiency and reduced urinary calcium excretion. This can be managed with initial generous intravenous fluid resuscitation with isotonic saline at a suggested initial rate of 4–6 L in the first 24 h and continued until volume repletion is achieved, although there are no randomised clinical trials to guide this practice [18].
Caution with fluid replacement should be made in those of advance age and with co-morbidities suggest congestive cardiac failure. Adjunctive loop diuretic therapy with furosemide can also additionally promote urinary calcium excretion but has been linked to volume depletion, electrolyte disturbances and metabolic acidosis there is also a paucity of high-powered evidence to support its use therefore it should not be routinely recommended [20,21]. Thiazide diuretics should be avoided as they increase calcium reabsorption at the renal tubular level.

If intravenous fluid resuscitation does not successfully restore calcium concentration, then intravenous bisphosphonates are recommended; common examples are pamidronate and zoledronate which work by suppressing bone resorption via osteoclast apoptosis. Bisphosphonates are widely used due to their favourable efficacy and toxicity profiles. Calcium concentration has a tendency to drop 2–4 days after therapy reaching a nadir at days 4–7 and remaining suppressed for up to 3–4 weeks [16]. Two large multicentre parallel randomized controlled trials compared 4 mg and 8 mg zoledronic acid to 90 mg pamidronate in managing hypercalcaemia of malignancy found significant differences in day 10 response rates and duration of response both favouring zoledronic acid as the superior agent [22]. Per European guidance zoledronic acid 4 mg over 15 min or pamidronate 30–90 mg (depending on severity of hypercalcaemia) or ibandronic acid 2–4 mg is recommended [18]. Disadvantages of bisphosphonate therapy include renal toxicity which can be addressed through dose adjustment and osteonecrosis of the jaw which is commonly seen in those with prolonged therapy course, poor dentition or recent invasive dental procedures [16,17].

In the US denosumab is approved for use of managing hypercalcaemia of malignancy in those who are poorly responsive to bisphosphonates. It is a monoclonal antibody directed against receptor activator of nuclear factor-KappaB ligand (RANKL) reducing osteoclast dedifferentiation and bone resorption. It may also be an option for those in whom bisphosphonates are contraindicated due severe renal impairment. Regular calcium monitoring is imperative as the risk for subsequent hypocalcaemia is high, particularly in those with reduced renal function [19]. In a single arm international study denosumab (120 mg once weekly for first month then once 4 weekly thereafter) was given to patients with hypercalcaemia of malignancy refractory to bisphosphonate therapy with a baseline calcium level of >12.5 mg/dL (3.1 mmol/L). Results revealed therapy reduced serum calcium levels in 64% of patients within 10 days with durable responses [23]. There is also recommendation for a once only dose of 60 mg subcutaneously or a weight-based dose of 0.3 mg/kg followed by re-dosing in one week if the patient remains persistently hypercalcaemic [9]. Studies have shown denosumab to be superior to zoledronic acid in delaying or preventing hypercalcaemia of malignancy in patients with advanced carcinoma stages and bone metastasis or multiple myeloma [24].

Calcitonin endogenously is produced by the parafollicular (c-cells) of the thyroid gland opposing the action of PTH and inhibits bone resorption as well as reducing renal tubular reabsorption of calcium. It is manufactured as a therapeutic agent with an onset of action within 2 h but short-lived effects with drug tolerance commonly developing within 2 days due to downregulation of calcitonin receptors [20]. Calcitonin is therefore best reserved for treatment under specialist supervision in the acute phase of hypercalcaemia whilst other therapies take effect. It is usually administered at a dose of 4–8IU/kg subcutaneously every 6–12 h; there are minimal side effects with the most common being nausea, vomiting and injection site pain [12]. No dose adjustments are required in those with renal failure [19]. A recent retrospective study reviewed patients on bisphosphonate therapy vs bisphosphonate therapy + calcitonin. This showed a larger decrease in corrected calcium concentration in the combination group at 48 h, however corrected calcium concentration in the first 72 h, time to normocalcaemia and clinical outcomes were similar indicating limited cost effectiveness of this therapy [25].

Corticosteroids is a useful therapy to consider particularly in the context of hypercalcaemia associated with multiple myeloma and other haematological malignancies caused by underlying 1,25(OH)$_2$Vit-D hypersecretion. Glucocorticoids inhibit the 1α-hydroxylase directed conversion of 25OH-VitD into its active metabolite thus reducing intestinal calcium absorption. They also have direct tumour lytic effects as well as inhibition of osteoclastic resorption by reducing the production of locally active cytokines [12]. Suggested regimens include prednisolone 40–60 mg/day for 10 days, often taking several days to reach desired effect but if therapy is proven to be ineffective after 10 days it should be stopped; reducing the risk of steroid-induced side effects and iatrogenic Cushing’s [9,17,19].
Cinacalcet is a calcimimetic agent which reduces PTH synthesis and secretion by activating the calcium sensing receptor (CaSR) on the surface of the parathyroid glands. Its indications include the management of hypercalcaemia in parathyroid carcinoma. A collection of case reports have conveyed benefits of Cinacalcet in reducing serum calcium burden when used in cases of humoral hypercalcaemia of malignancy although the precise underlying mechanisms remain unknown [26].

Dialysis or continuous renal replacement therapy should be considered in those patients with refractory hypercalcaemia to standard therapies and/or significant renal dysfunction or severe congestive cardiac failure. Dialysis against a dialysate containing little or no calcium is a proven reasonable and highly effective option for selected patients [10]. Notably, in an observational study there has been no association found between treatment with bisphosphonates, calcitonin or glucocorticoids and morbidity or mortality; indicating that the most appreciable benefits with traditional therapies may lie in symptomatic control [11].

**Paraneoplastic syndrome of inappropriate anti-diuretic hormone secretion (SIADH)**

**Definition**
This condition is characterised by excessive anti-diuretic (ADH) production (also known as arginine vasopressin – AVP) and is the second most common paraneoplastic endocrine syndrome [1]. It is denoted by hypo-osmolar euvoalaemic hyponatraemia and is diagnosed in around 1–2% of patients with a diagnosed malignancy [2]. SIADH is most commonly associated with small cell lung cancer (SCLC) (15%) but can also be seen with large cell lung cancer (LCLC). It is found in 2–4% of patients with non-SCLCs of prostate, breast, adrenal, pelvis, head & neck and lung carcinoids [1,3]. In admitted patients 14% of hyponatraemia cases can be attributed to an underlying malignant neoplasm and in a smaller subset of such it will precede tumour diagnosis [17]. Untreated paraneoplastic SIADH is linked to increased mortality and morbidity with the geriatric population most at risk. Hyponatraemia grade at short term follow up has also been shown to be predictive of long-term survival [3]. In patients with SCLC, SIADH is associated with higher risk of brain metastases, poorer treatment response, advanced disease stage and lower survival rates [2,27].

**Pathogenesis**
ADH is normally produced in the hypothalamus and stored in the nerve terminals of the posterior pituitary. Tumour cells can in vitro secrete ADH alongside oxytocin co-secretion and its associated neurophysins (carrier proteins) [8]. ADH and oxytocin can exert both paracrine and autocrine signalling activities and have been implicated in the initiation and growth of SCLCs, albeit cases of co-secretion have not been reported in the literature to the best of our knowledge [8]. Ectopic production of ADH from tumour cells has been identified in in vitro studies including the detection of high concentrations of immune-reactive ADH and ADH mRNA from tumour extracts [3]. Ectopic oxytocin secretion is a very rare PNS but has been reported in cases of SCLC by Shigetomi et al. and Wilson & Ngsee [8].

ADH binds to V2 vasopressin receptors in the renal collecting tubules increasing the reabsorption of free water via aquaporin2 water channels. This lowers the serum sodium concentration and leads to a hypo-osmolar state with a relatively high concentration of urinary sodium. Tumour cells have also been linked to the co-secretion of atrial natriuretic peptide (ANP) which can contribute to hyponatraemia through natriuresis [8].

**Historical perspectives**
The condition was first described in 1957 by William Schwartz and Frederic Bartter at separate institutions in two patients with lung cancer who developed hyponatraemia with urinary sodium loss. It was postulated that these tumours had led to the inappropriate secretion on ADH. Subsequent to this the Bartter-Schwartz diagnostic criteria were released in 1967 [17,28].

**Symptoms and diagnosis**
Associated symptoms depend on how quickly hyponatraemia occurs. With a serum sodium concentration of <125 mmol/L developing within 48 h (acute) then severe symptoms can be expected which include seizures, altered mental status, respiratory collapse, coma and death. In cases of slowly
progressive hyponatraemia mild symptoms occur which include nausea, vomiting, headaches, confusion/memory difficulties, fatigue and gait disorders [2].

The diagnostic criteria include the following: clinical euvolaemia, serum sodium <135 mmol/L, hyperosmolality <275 mOsm/kg, urine osmolality >100 mOsm/kg and increased sodium excretion in the urine. Based on European guidance the diagnostic urine sodium cut off value is > 30 mmol/L [29]. Cortisol is necessary for the efficient excretion of free water and thus glucocorticoid deficiency is important to exclude as it can lead to increased retention of free water and subsequent hyponatraemia. Similarly, hypothyroidism should be excluded as it can present with a similar pattern of hyponatraemia [2,17].

Treatment

The optimal treatment for paraneoplastic SIADH remains treatment directed towards the underlying tumour; if successful, sodium concentration could normalise within a matter of weeks [3].

Acute, severe hyponatraemia is a life-threatening emergency and should be managed with hypertonic saline (3%) 100 ml over 10 min (repeated 2–3 times if necessary) ideally in a high-dependency unit. Additionally hypertonic saline (1.8%) 1 ml/kg/h over 4–6 h has been recognised as an alternative therapy in acute (and chronic) hyponatraemia. Sodium concentration should not increase more than 4–6 mmol/L in the first 6 h [30].

For chronic hyponatraemia (>48 h) use of the *Furst formula* should be considered. This uses the sum of the urinary [Na+] and [K+]; where this is greater than the serum [Na+] fluid restriction alone if unlikely to be an effective strategy. A typical fluid restriction should commence at 500 ml/day less than the 24-h urine output [30]. Where fluid restriction is ineffective or unfeasible pharmacological therapies should be utilised. Demeclocycline interferes with the renal response to ADH, side effects include nausea, diarrhoea, renal toxicity and long-term use can lead to diabetes insipidus. Due to side effects and variable efficacy, demeclocycline is not routinely recommended for any degree of hyponatraemia [16,29]. Vasopressin receptor antagonists (e.g. Tolvaptan) form a newer class of drugs used in the management of SIADH blocking ADH receptor binding in the renal tubules leading to increased excretion of free water. In systematic review vasopressin receptor antagonists have been shown to be an effective treatment for both hypervolaemic and euvolaemic hyponatraemia but with an increased rate of rapid sodium correction [31]. In the last major European guidelines this drug class is not routinely recommended [29]. Regardless of treatment method gradual sodium correction of maximum 8 mmol/L per day is advised to reduce the risk of developing osmotic demyelination syndrome (ODS).

**Paraneoplastic Cushing’s syndrome**

**Definition**

Ocurs secondary to aberrant secretory action of adrenocorticotropic hormone (ACTH) from tumour cells and more rarely from corticotrophin-releasing hormone (CRH) secretion; contributing to approximately 10% of cases of Cushing’s syndrome [3]. SCLC accounts for at least 50% of cases of paraneoplastic Cushing’s syndrome while NETs account for most of the other cases including bronchial, thymic, pancreatic, phaeochromocytoma and medullary thyroid carcinoma (MTC). Rarely, other malignancies including breast, prostate, pelvic or haematological may be associated with paraneoplastic Cushing’s syndrome. Typically, serum ACTH and cortisol concentrations are higher in patients with associated SCLC than those with NETs [1]. Predictors of prognosis include tumour histology and severity of hypercortisolism signs and symptoms which are associated with increased morbidity and mortality. SCLC and thymic NETs induced paraneoplastic Cushing’s syndrome is associated with poorer prognosis [17].

**Pathogenesis**

ACTH is formed as a cleaved byproduct of the precursor hormone pro-opiomelanocortin (POMC). In this condition there is increased tumour expression on POMC due to ectopic activation of pituitary specific gene promoters. The processing of POMC in extra-pituitary tumours is often incomplete with the release of POMC fragments with reduced biological activity into the circulation. There is a high frequency of expression on POMC in SCLC and carcinoid tumours with only a very small proportion of patients developing the subsequent clinical syndrome of ACTH excess. The underlying mechanisms translating tumour POMC expression to clinical syndrome of ACTH excess is poorly understood [1].
form of poorly processed ACTH produced by certain tumors, which is a larger and more acidic peptide molecule than little ACTH, but is not immunochemically distinguishable from it and does not exert any of the biologic effects characteristic of ACTH proteolytic digestion of big ACTH yields hormonally active little ACTH [8].

**Historical perspectives**

Cases of Cushing’s syndrome diagnosed in association with extra-pituitary tumours were noted in 1928. The relationship between this syndrome and the ectopic tumour secretion of ACTH was only later confirmed through cases series in 1962 [27].

**Symptoms and diagnosis**

The clinical manifestations of hypercortisolemia are broad and affect multiple organ systems. Common clinical signs include weight gain (centripetal fat) albeit in some patients weight loss, plethora of face and neck, abdominal striae, proximal myopathy, peripheral oedema, hypertension, psychiatric disorders, osmotic symptoms (increased risk of diabetes mellitus), hirsutism, menstrual disorders, hypokalaemia and osteoporosis.

As per The Endocrine Society clinical practice guidance, those suspected of cortisol excess should be screened using the following 4 methods:

- Urine free cortisol (UFC) (two measurements).
- Late-night salivary cortisol (two measurements).
- 1-mg overnight Dexamethasone suppression test (ODST).
- Low-dose Dexamethasone suppression test (LDDST) (2 mg/d for 48 h) [32].

The high-dose Dexamethasone suppression test (HDDST) (8 mg over 1 or 2 days) can help distinguish between Cushing’s disease and ectopic ACTH production.

In confirmed cases there is an expectation of non-suppressed serum ACTH levels in the context of elevated and/or unsuppressed cortisol levels on dynamic testing. Metabolic disturbances including hypokalaemia, hyperglycaemia and alkalosis are common. Imaging studies are important to locate a tumour source and rule out any underlying adrenal/pituitary lesion which might include CT/MRI and somatostatin receptor nuclear imaging. Inferior petrosal sinus sampling to rule out a pituitary aetiology is not required but can improve diagnostic yield [16,17]. A definitive diagnosis is made with the demonstration of ACTH positivity on immunohistochemical staining of tumour cells and/or reversal of the clinical syndrome/hypercortisolemia after removal or debulking of tumour [17].

In contrast to paraneoplastic SIADH and hypercalcaemia, patients with paraneoplastic Cushing’s are more likely to present with endocrine symptoms before a neoplasm is identified; and similarly, symptoms relapse may indicate disease recurrence [16].

**Treatment**

The optimal treatment strategy remains those directed primarily towards the underlying tumour with paraneoplastic Cushing’s secondary to NSCLC responding well generally to systemic cytotoxic therapies. There is a lack of clinical trials or prospective studies comparing medical therapies directed towards the inhibition of steroidogenesis or glucocorticoid receptor antagonism to reduce the burden of hypercortisolism. These treatments may provide a bridge to those awaiting surgery or be used in patients not amenable to surgical intervention. Such therapies include ketoconazole, metyrapone, etomidate, mitotane, and mifepristone. Ketoconazole has been a widely accepted treatment option (usually commenced at a dose of 200 mg 2–3 times per day) due to better tolerance despite its links to hepatotoxicity, nausea and vomiting [27,33]. Tumours secreting ectopic ACTH may also express dopamine or somatostatin receptor therefore somatostatin analogues or dopamine agonists are occasionally used as standalone or adjunctive treatment [17]. If medical therapies fail bilateral adrenalectomies should be considered promptly to prevent the debilitating complications of hypercortisolism [3].

Nakajima et al. report a case of stage IV SCLC and ectopic ACTH syndrome (EAS) with good response and symptom resolution to a combination of carboplatin/etoposide and immune checkpoint inhibitor therapy with atezolizumab [34].
Non-islet cell tumour hypoglycaemia (NICTH)

Definition
The development of tumour mediated recurrent hypoglycaemia outside the realms of islet cell origin due to substances induced which interfere with glucose and insulin action/metabolism. Typically affecting elderly patients with advanced disease or mesenchymal origin tumours (sarcomas, GIST), renal, ovary, NETs. Occasionally, hypoglycaemic episodes may predate the diagnosis of the underlying tumour [16]. The incidence of NICTH ranges annually between 2.1 and 17 cases per million with an even distribution between genders [35].

Pathogenesis
NICTH is commonly associated with tumour production of IGF2 and notably ‘big’ IGF2 (molecular mass 10–17 kDa) due to incomplete glycosylation of precursor molecules. ‘Big’ IGF2 has a significant affinity for insulin receptor and this effect is potentiated by its reduced affinity to insulin growth factor binding protein 3 (IGFBP3) and subsequent increased bioavailability. IGF2 and its isoforms cause insulin receptor mediated hypoglycaemia leading to increased peripheral cellular glucose uptake, suppression of hepatic gluconeogenesis and inhibition of ketogenesis. Most tumours presenting with this syndrome are mesenchymal or epithelial in origin [8,35,36]. Typically, patients present with pronounced fasting hypoglycaemia.

Cases of NICTH induced by tumour secretion of IGF1 are extremely rare and limited to sparse case reports [37–39]. In a case by Nauck MA et al., a patient with metastatic large-cell lung cancer without features of acromegaly was noted to have elevated serum IGF1 with normal IGF2 concentrations. Tissue IGF1 was also identified with immunohistochemistry, in situ hybridization and by RT-PCR after RNA extraction. After chemotherapy IGF1 concentration normalised and hypoglycaemic episodes resolved [37].

Non islet-cell tumour ectopic insulin secretion is rare reported secondary to renal cell carcinoma and an ovarian tumour of mixed neuroendocrine and yolk sac origin in the literature [3,8].

Other tumour related factors include antibodies against insulin receptors, various cytokines (including TNF-α, IL-1, IL-6), catecholamines and glucagon-like peptide 1 (GLP-1) [3]. Additionally, hypoglycaemia may be related to direct tumour invasion into the liver or adrenals glands. Other complicating factors contributing to hypoglycaemia should be considered including renal failure, sepsis and malnourishment.

Historical perspectives
First described by Nadler and Wolfer as early as 1929 in a patient with hepatocellular carcinoma with suspicious hypoglycaemia in the absence of symptoms related to liver insufficiency [40].

Symptoms and diagnosis
Symptoms are sympathoadrenal and neuroglycopenia mediated and include diaphoresis, palpitations, tremors, blurred vision, confusion, drowsiness, impaired judgement, and coma.

Hypoglycaemia should be confirmed by Whipple’s Triad with the identification of neuroglycopenic symptoms, biochemical hypoglycaemia and the resolution of symptoms once hypoglycaemia has been corrected. NICTH is commonly associated with low insulin and c-peptide concentrations. In the realms of aberrant IGF-2 secretion additionally there is the identification of an elevated plasma IGF-2: IGF-1 ratio and suppressed ketone body formation in the form of β-hydroxybutyrate in the context of positive immunoblotting for “big IGF-2” from the resected tumour.

Treatment
Definite resolution is achieved via tumour directed therapies. In the acute setting glucagon, oral and/or intravenous dextrose can be utilised to manage hypoglycaemia (100 ml 20% dextrose infused over 15 min). The most common long-term therapy is glucocorticoids (Prednisolone 20–40 mg daily). Other therapies used to maintain glycaemic control include recombinant growth hormone (rGH) and octreotide. Diazoxide inhibits insulin secretion by pancreatic β cells and has traditionally been used to manage islet cell tumour hypoglycaemia however it has also been approved for the treatment of hypoglycaemia associated with hyperinsulinism in extrapancreatic malignancies [16].
Paraneoplastic acromegaly

Definition

Acromegaly associated with an extra-pituitary neoplasm represents a rare phenomenon constituting < 1% of overall cases. The syndrome is linked to ectopic secretion of growth hormone releasing hormone (GHRH) more commonly rather than growth hormone (GH) [13]. Ectopic secretion of GH has only been described in isolated cases [41,42] and this entity represents approximately 0.1% of paraneoplastic acromegaly cases [3]. Tumours most commonly associated with GHRH production include pancreatic NETs (pNETs), lung carcinoids, SCLC and pheochromocytomas. Ectopic GH production with associated clinical phenotype is rare but is described in case reports [1].

Pathogenesis

GHRH acts through binding to its receptors on somatotroph cells which activates adenylate cyclase with a subsequent increase in intracellular cyclic AMP causing the release of GH into the circulation. Acromegaly ensues from a downstream increased release of IGF-1 from the liver exerting its effects on peripheral tissues and organs [17].

Historical perspectives

Evidence for the existence of ectopic GH secretion dates back to clinical observation from 1960. It was then noted that rare cases of carcinoids (especially those of bronchial tree) were associated with phenotype of GH excess. In 1976 it was noted that this syndrome resolved after surgical excision of carcinoid. In 1984 the main biological activity of GHRH was found to be in its first 29 amino acids with tumour and hypothalamic forms both sharing the same amino acid sequence [17].

Symptoms and diagnosis

Symptoms correspond to those expected in GH secreting pituitary adenomas. This includes sweating, arthralgia, headaches, skin thickening and weakness, with a predisposition towards hypotension and glucose intolerance [2].

Diagnosis also follows principles used in pituitary adenomas. An oral glucose tolerance test (75g) should be employed to demonstrate lack of suppressible GH. Plasma GHRH concentration has high levels of specificity for diagnosis (using a threshold of 250–300 ng/L) and significant elevations can be expected in this syndrome; although this test is not readily available in many centres, it can prove to be a good tool for follow up [2,3]. MRI imaging should be used to exclude a somatotroph pituitary adenoma instead one can expect a normal or diffusely enlarged pituitary gland. Somatostatin receptor scintigraphy has also been used successfully in the diagnosis of this syndrome [43].

Treatment

Definitive treatment should be directed to the primary tumour and after surgical excision, normalisation of GH concentration can be anticipated within the first weeks. Systemic therapy is required in those with metastatic or inoperable disease including the use of chemotherapy and somatostatin analogues [17]. Pasireotide a newer somatostatin analogue binding to 4 of 5 somatostatin receptors may provide an effective treatment option especially for those poorly responsive to first generation somatostatin analogues as supported by recent clinical trial data in patients with GH excess secondary to pituitary adenoma [2,44].

Less common endocrine paraneoplastic syndromes secondary to peptide hormones

Ectopic renin secretion

Cases of ectopic renin secretion from extra-renal tumours remain a rare occurrence. There are approximately 30 case reports in English literature since 1977 including carcinoma of the pituitary,
orbit, lung, liver, adrenal gland, ovary, testes, pancreas and small intestine \cite{1,45–47}. Clinical implications of excess renin production include hypertension, hyperkalaemia and metabolic alkalosis. There is an increased ratio of pro-renin to renin occurring as a result of inefficient processing of renin by the tumours \cite{1,3}. This PNS is characteristic of elevated plasma renin activity (PRA) and aldosterone levels with improvement after cytotoxic therapy/surgery. Features of renin immunoreactivity can also be expected immunohistochemically. In a case of ileal carcinoma by Saito T et al. 1989 the first demonstration of renin mRNA from tumour tissue was described \cite{46}. Adjuvant use of various anti-hypertensives, spironolactone or rarely aliskiren has proven to be helpful in offering temporary symptom relief \cite{3}.

**Ectopic \( \beta \)-human chorionic gonadotrophin (\( \beta hCG \)) secretion**

Tumour secretion of \( \beta hCG \) is an uncommon occurrence. Several cases reports exist with sources including pulmonary, gastrointestinal, hepatocellular, gynaecological and genitourinary malignancies \cite{1}. This PNS has also been identified in sarcomas, melanomas, adenocarcinomas, squamous cell cancers, non-small cell lung cancer (NSCLC), extragonadal germ cell tumours (EGCTs) and haematopoietic neoplasms \cite{1,48–53}. More recently by de Sousa MD et al. 2021 in a case of pulmonary pleomorphic carcinoma (PPC) there were elevated serum \( \beta hCG \) levels as well tumour immunopositivity for \( \beta hCG \); this combination of findings in lung cancer appears to be related to a more extensive stage of disease, chemo-resistance and poorer prognosis \cite{54}. Clinically this PNS is associated with gynaecomastia in men, menstrual irregularity and virilisation in women, and precocious puberty in children; including a case of a 5-year old girl with a pinealoma \cite{3,55}. A \( \beta hCG \)-like protein is also present in normal tissues with some data to support the view that the alpha chain of hCG may have a paracrine effect on the growth of tumour cells \cite{1}. Definitive treatment is centred on tumour resection or multi-agent chemotherapy in sensitive malignancies such as SCLC \cite{3}.

**Ectopic gonadotrophin secretion**

Ectopic gonadotrophin secretion remains a rare entity, reported within a small collection of case reports. These include cases of ectopic follicle stimulating hormone (FSH) hypersecretion leading to presentation with ovarian hyperstimulation syndrome (OHSS) and additionally cases of luteinising hormone (LH) hypersecretion resembling presentation with polycystic ovarian syndrome \cite{3,56}. Notable presenting clinical features include irregular menses, infertility and precocious puberty \cite{1}. In an interesting case by Brignardello E et al. 2004, a 61 year old male presented with clinically significant LH, 17\( \beta \)-estradiol, testosterone and haemoglobin elevation on the background of a pancreatic NET which resolved biochemically and symptomatically post-surgery \cite{57}.

**Other rare peptide hormone secretion**

Ectopic prolactin secretion has been described with patients presenting with galactorrhoea or hyperprolactinemia. Neoplasms associated with paraneoplastic hyperprolactinaemia are SCLC and commonly neoplasms of the female reproductive system including leiomyomas and uterine tumour resembling ovarian sex cord tumour (UTROSTC) \cite{58–60}. Ectopic TSH secretion is extremely rare and has previously been linked to ectopic pituitary adenomas with documented hormonal co-secretion, responsive to octreotide \cite{3,61}. PNS associated with gastroenteropancreatic peptides is very rare with implicated hormones including: vasoactive intestinal peptide (VIP), glucagon-like peptides 1 and 2 (GLP-1, GLP-2), polypeptide YY (PYY), gastrin, gastrin-releasing peptide (GRP), cholecystokinin (CCK) and ghrelin both from NETs and non-NETs. Other rare hormones identified in PNS include calcitonin, human placental lactogen (hPL), neureotensin, somatostatin, glucagon, oxytocin and fibroblast growth factor (FGF23) — linked to the development of osteogenic hypophosphatemic osteomalacia (or tumour-induced osteomalacia) \cite{1,3}.
Endocrine paraneoplastic syndromes secondary to non-peptide hormones

Cytokines

The release of cytokines from tumour cells is implicated in inflammatory related PNSs primarily associated with features of pyrexia, fatigue, weight loss and cachexia [8]. The major pyrogenic cytokines implicated from tumour cells include interleukin 1 (IL-1), interleukin 6 (IL-6), tumour necrosis factor (TNF-α) and interferon. Cytokines can produce infectious or neoplastic fever in those with cancer; activating preoptic nuclei of the hypothalamus to raise the set point of body temperature through the activation of prostaglandin E2 [62]. In a systematic review, a consistent pattern of cytokine activation was observed in various malignancies with specific cytokines concentration being associated to patient prognosis [63]. TGFβ suppresses anti-tumour immune responses and TNF-α has a suggested role in the growth of tumours therefore monoclonal antibody based treatments countering these cytokines have been explored in pre-clinical and clinical trials as potential anti-cancer management including Luspatercept and Bintrafusp alfa [64,65].

Steroid related compounds

PNS related steroid secretion is rare, particularly in the context of non-gonadal/non-adrenal tumours, thought to cause significant morbidity as a result of steroid excess [65]. Mesenchymal stem cells can differentiate into steroidogenic cells following the ectopic expression of nuclear receptor (NR) 5A subfamily proteins; steroidogenic factor-1 and liver receptor homolog-1 [66]. This could represent one of the mechanisms underlying the development of PNS including rare cases of steroid producing tumours from tissues other than adrenal or gonads. Cases of paraneoplastic hyperaldosteronism are also rarely described with potential underlying links to the expression of the CYP11B2 gene [3].

Pituitary autoimmunity

Anti-Pit-1 hypophysitis

Paraneoplastic pituitary autoimmunity is a novel clinical entity which presents hypophysitis through non-traditional pathways. Pit-1 is a transcription factor essential for the function of specific pituitary cells types. It has been found that tumours expressing Pit-1 or POMC/ACTH may lead to tumour mediated overproduction of anti-Pit-1 and anti-ACTH antibodies [67].

An anti-Pit-1 syndrome was first described in 2011 and leads to a hypophysitis characterized by combined acquired deficiencies of growth hormone, prolactin and TSH [68]. Six cases of paraneoplastic anti-Pit-1 genesis have been described in the literature in patients aged 44–85 mostly on the background of thymoma with other causes including bladder lymphoma and metastatic cancer of unknown primary. Detection of circulating anti-Pit-1 autoantibodies were found in all but one case with MRI imaging revealing either a normal or slightly atrophic pituitary gland [69]. In line with previous cases anti-Pit-1 antibodies can be measured by immunoblotting analysis or specific enzyme-linked immunosorbent assay; and Pit-1 reactive T cells which play a pivotal role in the development of the disease can be measured by enzyme-linked immunospot (ELISpot) assays. Pit-1 protein positivity is detected through tumour immunohistochemistry [69,70]. CD8+ cells have been found to infiltrate the pituitary gland in this PNS indicating Pit-1-reactive cytotoxic lymphocytes (CTLs) rather than anti-Pit-1 antibodies as playing a pivotal role in pathogenesis [69]. Epigenetic patterns including altered DNA methylation may be associated with aberrant Pit-1 expression in thymoma tissues [69,71].

Isolated ACTH deficiency

Isolated acquired ACTH deficiency (IAD) has also been postulated as a rare novel endocrine PNS [72]. In a case of a 42-year-old lady with an illness anxiety disorder (IAD) diagnosis and 3 years later diagnosed with large cell neuroendocrine carcinoma (LCNEC) of the lung, LCNEC tissues revealed
ectopic ACTH secretion as well as lymphocytic infiltration. In addition, anti-POMC antibodies were detected in serum with a lymphocytic reaction towards POMC protein and a finding of CD8+ cells residing adjacent to pituitary corticotrophs — all indicating autoimmunity [73]. Several cases of IAD in the presence of malignant tumours have been previously described including on the background of gastric carcinoma and acute lymphoblastic anaemia, but autoimmunity was not specifically investigated in these cases [73–75]. Although several autoimmune mechanisms have been suggested the precise aetiology of IAD remains largely unknown, with recent evidence suggesting that potential occult tumour mediated autoimmunity should be considered in cases of unexplained IAD [71].

There is evidence that patients with anti-PIT-1 hypophysitis or with isolated ACTH deficiency did not recover from pituitary hormone deficiencies after resection of thymoma or LCNEC. This is likely due to irreversible damage to pituitary cells by CTLs; thus, early detection and immunosuppressive therapy may be pivotal to preventing long-term disease development.

Summary

PNSs represent a rare and likely under-recognized group of disorders. As the incidence of several types of neoplasms increases, and as patients live longer due to therapeutic advancements, the incidence of PNS will most probably increase. Early recognition and management of 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. Due to the rarity of PNS and nature of patient cohorts, clinical trials are difficult to design. Nevertheless, further research and formalised up-to-date international guidelines are warranted to create optimized treatment regimens as PNS management is likely to vary considerably between institutions. The specific underlying cause of PNS remains unknown with stem cell theory remaining popular, allowing the activation of hormone related genes after genetic and epigenetic changes under specific conditions. PNS mediated pituitary autoimmunity represents an interesting new area in the field; the development of novel immunosuppressive therapy may provide benefit here and in cytokine medicated syndromes.

Practice points

- PNS remission is best achieved through definitive anti-tumour therapy
- PNS presentation may pre-date underlying neoplasia diagnosis
- Supportive therapies in PNS have a role in symptom management, palliative care and may improve morbidity and mortality
- Hypercalcaemia remains the most common form of PNS. In Humoral Hypercalcaemia of Malignancy expect suppressed PTH levels and elevated PTHrP levels (rarely needs to be performed)

Research agenda

- The exact prevalence of PNS is still a matter of debate, registration of these syndromes into large multinational registries seems imperative to help identify their exact aetiology and their effect on the disease process.
- Update to major European guidelines is required to reflect the growing role of vasopressin receptor antagonists (e.g. Tolvaptan) in the management of SIADH
- Multicentre randomised clinical trials are necessary to explore optimal medical therapies for the management of PNS including paraneoplastic Cushing’s, acromegaly and hypoglycaemia
- Further research into the pathophysiology of PNS related pituitary autoimmunity in combination with the role of immunosuppressive therapeutic options is a promising novel area
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References


