Endocrine Paraneoplastic Syndromes: A Review

Abstract
Paraneoplastic endocrine syndromes result from ectopic production of hormones by different tumors. Hypercalcemia of malignancy is the most common, mostly caused by ectopic parathyroid hormone related peptide (PTHrP) production which increases bone resorption. Other causes include the rare ectopic parathyroid hormone (PTH) production, ectopic production of 1, 25-(OH)2 vitamin D by the tumor and its adjacent macrophages and bone metastasis which by itself in addition to the local production of PTHrP at the level of the bone lead to bone resorption and thus hypercalcemia. Treatment includes extracellular fluid volume repletion, bisphosphonates or denosumab and calcitonin. Ectopic Cushing’s syndrome caused by ectopic ACTH production results in hypokalemia, proximal muscle weakness, easy bruising ability, hypertension, diabetes and psychiatric abnormalities including depression and mood disorders. Different diagnostic measures help to differentiate Cushing’s disease from ectopic Cushing’s syndrome. Treatment includes surgical resection of tumor and medical therapy to suppress excess cortisol production. Ectopic secretion of ADH has been associated with different tumor types. The best treatment options include removal of the underlying tumor, chemotherapy, or radiotherapy in addition to free water restriction, demeclocycline and vaptans. Ectopic growth hormone releasing hormone secretion has been identified with carcinoids, pheochromocytoma and other tumors. Surgery is the mainstay of therapy with systemic therapy used in metastatic disease. Other rare ectopic hormone syndromes have also been identified including ectopic prolactin, ectopic erythropoietin, and thrombopoietin in addition to others.

Keywords
Ectopic Hormones; Hypercalcemia Of Malignancy; Tumors; Parathyroid Hormone Related Peptide; Bisphosphonates; 1,25-Dihydroxyvitamin D; Glucocorticoids; Calcitonin; Parathyroid Hormone; Ectopic Cushing Syndrome; Hyponatremia; Syndrome Of Inappropriate Antidiuretic Hormone Secretion; Ectopic Growth Hormone Releasing Hormone Secretion; Acromegaly; Ectopic Prolactin Secretion; Tumor Induced Osteomalacia

Abbreviations
RANKL: Receptor activator of nuclear factor- kappa B ligand; PTHrP: Parathyroid Hormone Related Peptide; ACTH: Adrenocorticotropic Hormone; POMC: Pro-Opiomelanocortin; PNES: Paraneoplastic Endocrine Syndrome; OPG: Osteoprotegrin; CS: Cushing’s Syndrome; CLIP: Corticotrophin-Like Intermediate Lobe Peptide; MSH: α-Melanocyte Stimulating Hormone; CLIP: Corticotrophin-Like Intermediate Lobe Peptide; EAS: Ectopic ACTH Syndrome; NSE: Neuron-Specific Enolase; GHRH: Growth Hormone Releasing Hormone; ADH: Antidiuretic Hormone; AVP: Arginine Vasopressin; SIADH: Syndrome of Inappropriate ADH Secretion; GHRH: Growth Hormone Releasing Hormone; CRH: Corticotropin Releasing Hormone; PRL: Prolactin; CEA: Carcinoembryonic Antigen

Introduction
The paraneoplastic endocrine syndromes (PNES) occur as a result of the production of hormonal substances by different tumors leading to the manifestation of unique clinical endocrine syndromes. Development of these disorders does not often necessarily correlate with the cancer stage or prognosis and may even occur before the diagnosis of cancer is made. For the diagnosis of ectopic hormone syndromes to be made, there must be clinical or biochemical evidence of an endocrine abnormality in a patient with neoplastic disease, without any concomitant native endocrine organ dysfunction that might explain the syndrome as well. Endocrine syndrome often disappears after tumor removal, suggesting that the tumor was the source of the ectopic hormone production. A high hormonal arteriovenous gradient is usually present across the tumor. However owing to practical reasons and the unpredictable hormone secretion by the tumor, this criterion is not always available. Moreover the lack of precision and the fact that the hormone assays are sensitive may cause problems in evaluating the results as well. Tumor cells that are cultured may be capable of synthesizing the hormone or contain higher concentration of hormone-specific mRNA. However, it is important to mention that even normal non-endocrine tissues are capable of producing hormones, such as the production of Propiomelanocortin (POMC) by certain non-endocrine tissues. Treatment of the malignancy itself is the mainstay of treatment of paraneoplastic endocrine syndromes, along with other supportive measures such as fluid resuscitation or electrolyte disturbance correction [1].

It is important for the endocrinologist and oncologist to recognize these paraneoplastic endocrine syndromes since this may help in defining the cancer type and hence lead to the appropriate management. In addition, these syndromes are a major cause of morbidity and mortality. Moreover,
paraneoplastic endocrine syndromes may be the first presenting feature of malignancy [23]. This paper provides an overview on the common PNES, their prevalence, diagnosis, prognosis and response to treatment (Table 1).

Methodology of Literature Search

Eligible studies were identified by a search, from year 1920 up till February 2014, in Medline, PUBMED and EMBASE using a refined search strategy with several terms used including “endocrine paraneoplastic syndromes”, “ectopic hormones”, “humoral hypercalcemia of malignancy”, “ectopic parathyroid hormone related peptide”, “ectopic ACTH”, “ectopic Cushing syndrome”, “ectopic antiurietic hormone”, “syndrome of inappropriate ADH”, “ectopic growth hormone releasing hormone”, “ectopic growth hormone”, “ectopic prolactin”, “ectopic thyroid stimulating hormone” in addition to several others. In addition, searches of personal collections and the reference lists of eligible studies were identified with their full text papers being retrieved.

A-Hypercalcemia of Malignancy

**Historical Perspective:** The first description of the term ‘hypercalcemia of malignancy’ occurred in 1924 [4]. Then in 1936, a case of a 57-year-old male with bronchogenic carcinoma with marked hypercalcemia, not associated with metastases as evident radiologically or at postmortem, and with normal parathyroids, was reported by Gutman et al. [5] who attributed the cause to “complicating factors as yet wholly obscure”. In 1941, Albright reported another case of a 51 year old man with lytic lesion in his right ilium, which was metastatic from renal cell carcinoma, who had hypercalcemia & hypophosphatemia. Hypercalcemia resolved after irradiation of this single bone metastasis. Since lysis of bone is expected to liberate both calcium and phosphate, Albright suggested that tumor was producing parathyroid hormone (PTH) and the term ectopic PTH syndrome was used [6]. But then with the improvement of PTH radioimmunooassay in the 1970s, some doubt arose regarding PTH being the cause for this syndrome. The term “humoral hypercalcemia of malignancy” was first proposed in 1979 by Martin and Atkins, in patients who exhibited increased renal production of cAMP with a low or undetectable plasma levels of PTH [7]. Sensitive bioassays were able to identify and purify this “PTH-like factor” which later was called parathyroid hormone related peptide (PTHrP). Its sequence was finally obtained in 1986, from a cultured human squamous cell line, obtained from a patient who had hypercalcemia [8].

**Prevalence, presentation and diagnosis:** Hypercalcemia of malignancy is the most common PNES, where it is estimated to occur in up to 30% of patients with cancer at some point during their course of disease. It is the most common cause of hypercalcemia in hospitalized patients as opposed to primary hyperparathyroidism being the most common cause of hypercalcemia in community at large. It conveys a poor prognosis, where in a retrospective study of 126 patients with cancer-associated hypercalcemia, the median survival did not exceed 30 days [9]. In a cohort of 252 patients, a prognostic score including liver metastasis, squamous cell carcinoma, hypoalbuminemia, and calcemia >2.83 mmol was developed, for the prediction of 90-day mortality in patients with hypercalcemia of malignancy, and it was found that those patients who had a score of 0 experienced a median overall survival of 797 days as opposed to those having a score of ≥1, who were shown to have a median survival of 49 days only [10]. Hypercalcemia of malignancy occurs most commonly in primary tumors of lung, breast, head and neck, kidney and ovary. Hematological malignancies can be complicated by hypercalcemia as well, where up to one third of patients with multiple myeloma were found to have high calcium levels. Malignancy associated hypercalcemia is rapidly progressive and symptoms tend to occur at lower plasma concentrations of calcium, where it was estimated that around 50 % of patients develop neurological manifestations. The causes of death in these patients is mainly related to the complications of hypercalcemia such as coma, renal failure, and to the progression of tumor itself [11].

**Pathophysiology:** There are four principal mechanisms of hypercalcemia in cancer patients [11,12]. (Table 2) Parathyroid hormone releasing peptide (PTHrP) secretion by tumor cells, accounts for 80% of cases and occurs with squamous cell tumors mainly [13-16]. PTHrP is a small peptide, which resembles parathyroid hormone (PTH) where 8 of its first 16 amino acids are homologous to PTH. Like parathyroid hormone (PTH), the bioactivity of PTHrP resides mainly in these first eight amino acids. PTHrP acts on the kidney leading to increased vascular tubular reabsorption of calcium. Indeed, it is common to ascribe the clinical syndrome of PTHrP production to hyperparathyroidism, until the identification of a suppressed parathyroid hormone blood level. It is also capable of binding to PTH type 1 receptors normally located in bones, leading to increased bone resorption. It also enhances the production of RANK ligand (RANKL) by osteoblastic stromal cells, which acts as a powerful inducer of osteoclast formation and differentiation [17-20]. PTHrP also inhibits the production of osteoprotegerin (OPG). OPG is a secreted member of the tumor necrosis factor (TNF) receptor family that is produced by osteoblastic stromal cells, and is capable of inhibiting osteoclast formation. PTHrP, by inhibiting OPG production, would actually lead to increased osteoclast formation and differentiation and hence increased bone resorption. Indeed, it is common to ascribe the clinical syndrome of PTHrP production to hyperparathyroidism, until the identification of a suppressed parathyroid hormone blood level. It is important to mention that although PTHrP resembles PTH in its action in general, however it is not known to increase 1α-hydroxylase activity like parathyroid hormone does and hence 1,25-(OH)2D production does not increase in cases of hypercalcemia of malignancy when it is attributed to PTHrP production [11].

Extensive bone metastasis by the cancer cells would lead to local osteolysis and bone destruction. This accounts for approximately 20% of all the cases of hypercalcemia associated with malignancy. But recently there was growing body of evidence which revealed the importance of the local production...
of PTHrP by the invading cancer cells, which led to around 80% of causes of hypercalcemia in such patients with metastatic bone disease, especially in patients with breast cancer who had skeletal metastasis [21]. Therefore local PTHrP production might contribute to the ability of breast cancers to erode bone and cause metastases [22-24]. PTHrP levels were also found to be elevated in 64% of patients with hypercalcemia who had metastatic malignancy to bone from primary sources other than the breast tissue. Prostate cancers can also metastasize to bone leading to osteolytic and/or osteoblastic lesions as well [25-26]. Human T-cell leukemia virus type 1 (HTLV-1) associated adult T-cell leukemia/lymphoma was also associated with humeral hypercalcemia of malignancy [11].

Hypercalcemia was also found to occur in one-third of multiple myeloma patients. These patients were found to have increased bone resorption by the normal osteoclasts residing in the areas near to the myeloma cells [27]. This suggested that myeloma cells secrete factors that stimulate osteoclast action. Several cytokines have been postulated to be responsible for the increased bone resorption. These included TNF alpha, IL-1, and IL-6. Elevated PTHrP levels were found in one-third of patients with multiple myeloma who have hypercalcemia. PTHrP can be added to the list of cytokines contributing to the bone loss and hypercalcemia in patients with multiple myeloma [28].

As noted PTHrP is responsible for the vast majority of of humoral hypercalcemia of malignancy cases, however, rare cases have reported ectopic PTH secretion by tumors, where the suspicion of such cases should arise in a patient with a known malignancy that has an elevated calcium and PTH, and when a standard technetium (99mTc) sestamibi scan does not identify a parathyroid adenoma in the neck [11,12]. Hematological malignancies may also be associated with hypercalcemia, due to the excessive secretion of 1, 25-dihydroxyvitamin D, leading to the increased gastrointestinal absorption of calcium. This has been described in around half of all patients with lymphoma who were found to have hypercalcemia. In these patients, 1α-hydroxylase was found to be produced by tissue neighboring macrophages and by the lymphomatous tissues themselves [29]. These patients often have a normal or slightly increased phosphorus level (caused by the suppression of PTH production and increased phosphate reabsorption by the 1α, 25-dihydroxyvitamin D3), hypercalcemia and hypercalciuria, absence of bone metastasis, and an elevated serum calcium level.

**Treatment:** Dehydration is a common finding in hypercalcemic patients in general. Therefore the initial management of malignancy associated hypercalcemia does not differ from the management of other causes of hypercalcemia. It should include fluid resuscitation in the first instance with the infusion of a solution of normal saline at rates ranging between 100 and 300 mL/h. This will normally lower the serum calcium by 10% to 40% over a period of 6 to 12 h. Loop diuretics can also facilitate renal calcium excretion through inhibition of calcium reabsorption in the thick ascending limb of the loop of Henle, but should only be used after adequate hydration was done, otherwise dehydration will be worsened [13,30-33].

**Bisphosphonates:** Patients with severe hypercalcemia, with a serum calcium concentration level above 13 mg/dL, or those who have an altered level of consciousness or evidence of renal dysfunction attributable to hypercalcemia, should also be treated with bisphosphonates in addition to the generous intravenous hydration. Bisphosphonates suppress bone resorption by causing osteoclast apoptosis after inducing changes in its cytoskeleton [34-36]. They also induce apoptosis of tumor cells as shown by different in vitro and animal studies [37-39]. The bisphosphonates calcium lowering response was unfortunately short-lived and serum calcium usually returns to its high basal values within 2-4 weeks of discontinuing treatment in untreated malignancy cases. Pamidronate has been the most widely investigated bisphosphonate in the management of malignancy-associated hypercalcemia, with the recommended single dose of 90 mg, which was shown to achieve normocalcemia in up to 90% of patients regardless of tumor type or the presence or absence of bone metastases [40-42]. A recently published large multicenter double-blind study compared the efficacy of zoledronate and pamidronate in patients with malignancy-associated hypercalcemia and showed the superiority of zoledronate, which was administered as a single 5-min infusion of 4 mg (as initial treatment) or 8 mg (for relapsed or refractory hypercalcemia), as compared to pamidronate which was administered as a single 2-h infusion of the 90-mg dose. Zoledronate and pamidronate given at the above doses were found to decrease serum calcium concentrations to 2.7 mmol/L or below in 88% and 70% of patients, respectively. Zoledronate had also a longer lasting effect than pamidronate (30 days versus 17 days, respectively). There was, however, no difference in the retreatment response rate, which was 52% for both bisphosphonates [43]. Therefore, many clinicians prefer zoledronic acid for such cases. The bisphosphonate ibandronate is not yet approved by the FDA for this indication [44]. Disadvantages of bisphosphonates include renal toxicity which can be minimized with dose adjustment, osteonecrosis of the jaw, especially in patients with poor dentition and the risk of atypical fracture of the femur [45-46]. It is important to note that severe or refractory hypercalcemia which is unresponsive to different therapies is an indicator of poor prognosis.

**Denosumab:** Denosumab, a human monoclonal antibody targeting RANKL ligand, was first approved by the U.S. Food and Drug Administration (FDA) for its use in postmenopausal women with osteoporosis. Then in November 2010, it was used for the prevention of skeleton-related events in patients with solid tumors and bone metastases [47,48]. Denosumab was found to be superior to zoledronic acid in delaying or preventing skeletal-related events in patients with breast cancer who had metastases to bone [49]. In 2011, several clinical trials were undergone for investigating its role in giant cell tumors, multiple myeloma with bone metastases, and hypercalcemia of malignancy. A series of seven patients who received doses of denosumab for hypercalcemia of malignancy was reported. In this series the most common tumor types were breast cancer (n=3) and hematologic malignancies (n=2). All patients had bone involvement. Two of those patients received single doses of denosumab, the 60 mg
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reported to occur in around 25% of those patients [60].
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size ranged from 0.3 cm to 7 cm [60]. Presenting symptoms
are similar to those of Cushing disease. Psychiatric disorders
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ACTH syndrome occurs earlier in small cell lung carcinoma and
pancreatic islet cell tumors because of the early appearance of
symptoms related to ectopic ACTH production, as compared to
bronchial carcinoids which are more indolent and hence are
diagnosed at a later stage [61,62]. The experience with patients
who had ectopic Cushing syndrome, during the years 1985 to
2006, were retrospectively reviewed at a tertiary care center in
Chandigarh. It was found that weight loss (41.7%) was the most
common symptom followed by infections (16.7%). Hypertension
(100%), easy bruising (92%) and proximal myopathy (83%) were
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The hallmark of ectopic ACTH syndrome is the finding of
an increased plasma ACTH concentration, where a plasma
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differentiation between pituitary ACTH production and ectopic
tumor production of ACTH or ectopic CRH production is a very
difficult task. The oncologist who is confronted with a patient with
a malignant neoplasm and clinical features of Cushing syndrome
should not assume that these clinical features are due to a
diagnosis of ectopic ACTH syndrome without considering other
diagnostic possibilities including a pituitary ACTH producing
tumor. The diagnosis of ectopic ACTH syndrome can be made
after the demonstration of ACTH immunohistochemical staining
in the tumor tissue or in its metastatic deposits and/or reversal
of the clinical syndrome, with complete/partial resolution of the
hypercortisolemia syndrome after tumor resection, if a tumor
was identified in the first place. Pituitary adenomas are known
to retain some responsiveness to the negative feedback effects
of glucocorticoids, as opposed to ectopic tumors [62,63]. The
corticotropin-releasing hormone (CRH) test done either alone or
in combination with desmopressin in addition to the high-
dose dexamethasone test (HDDST) are the two most commonly
used dynamic tests to separate between the available entities.
Endogenous cortisol production which is not be suppressed with
the administration of high-dose dexamethasone and could not
be stimulated with the administration of corticotropin-releasing
hormone, suggest the diagnosis of Cushing’s syndrome resulting
from the ectopic secretion of corticotropin [60-63]. The next step
in the diagnostic work-up depends on the availability of bilateral
inferior petrosal sinus sampling (BIPSS) with CRH stimulation,
which also can help in the differentiation of causes of ACTH-
Inappropriate
secretion of ACTH in certain types of malignancies is uncommon
but still is an important cause of morbidity and mortality.
20% of cases of ACTH dependent Cushing’s syndrome are due
to ectopic ACTH syndrome (EAS) secretion. Small cell lung
cancers, medullary thyroid cancers and bronchial carcinoids
represent the tumors that are most commonly associated with
ectopic ACTH syndrome [56]. The previous literature reported
the high prevalence of ectopic ACTH syndrome caused by
small cell lung carcinoma but recently there has been shift
towards neuroendocrine tumors contributing to the ectopic
ACTH syndrome particularly the bronchial carcinoids. Other
tumors that are less likely to be associated with EAS include
islet cell tumors of the pancreas or pancreatic carcinoids, thymic
carcinoids, and gastrinomas [57-59].

Occult tumors, defined as those that cannot be identified even
after a meticulous diagnostic workup is done, contributed to 12-
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Calcitonin: Since calcitonin receptors are expressed on the
membrane surface of mature osteoclasts, and since receptor
activation directly and potently inhibits osteoclast function,
calcitonin was used for hypercalcemia of malignancy and is
known for its rapid calcium-lowering effect, which is maximal
4–6 h after injection. The effect of calcitonin is short-lived, where
serum calcium generally returns to pretreatment levels within
24 hours. As calcitonin acts rapidly but its effect is not sustained,
maximum beneficial effect is obtained by combining this agent
with a slower-acting bisphosphonate. The recommended dose of
calcitonin is 200 to 400 units intramuscularly or subcutaneously
every 12 hours [52,53].

Glucocorticoids: Glucocorticoids are useful in the
management of patients with hematological malignancies,
especially multiple myeloma patients because of their ability to
reduce the synthesis of bone-resorbing cytokines. They
may inhibit the growth of neoplastic lymphoid tissue in
lymphoreticular malignancies. They may reduce the production
of the active metabolite of vitamin D, hence normalizing serum
calcium in lymphomas patients by blocking its effects on
intestinal absorption of calcium [54]. Prednisone at a dose of 40–
60 mg daily is typically effective. However it is important to note
that if no appreciable response is observed within 10 days, then
glucocorticoid therapy should be discontinued. Moreover there
is a risk of inducing iatrogenic Cushing with the extensive use of
steroids [55].

B- Ectopic Cushing Syndrome

Prevalence, presentation and diagnosis: Inappropriate
secretion of ACTH in certain types of malignancies is uncommon
but still is an important cause of morbidity and mortality.
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The source of ectopic ACTH secretion should be established because the excision of an ACTH producing tumor can be curative. Conventional imaging studies, such as CT and MRI, may identify the tumor in only 50% of cases [63]. Functional imaging studies such as PET and somatostatin receptor scintigraphy (SRS) are complementary imaging tools [68-70]. Somatostatin receptor scintigraphy might be considered superior to PET in detecting bronchial carcinoids, especially that these tumors specifically are known to have low proliferation index [69,70].

Characterization of ACTH Related Peptides in Ectopic Cushing’s Syndrome: ACTH is formed as part of pro-opiomelanocortin (POMC), which is cleaved by prohormone convertase (PC) 1 at the C-terminal of ACTH to give β-LPH and then it cleaves the N-terminal of ACTH. Cleavage to smaller peptides occurs by the action of prohormone convertase 2 (PC2) with further post-translational modification to produce α-melanocyte stimulating hormone (αMSH). The extent of POMC processing is tissue dependent. In the anterior lobe of the pituitary, the presence of PC1 and the absence of PC2 results in ACTH as the major secretory product [71]. Although having an ACTH level above 200 ng/l is more common in ectopic CTH syndrome, no thresholds are definite for the distinction between EAS and Cushing disease [72-73]. Retrospective analysis of 86 patients found that measurement of mature ACTH was not helpful in the differential diagnosis between patients with pituitary-dependent Cushing’s disease and the ectopic ACTH syndrome. However measurement of ACTH precursors was helpful, as all patients with ectopic tumors that secrete ACTH were also found to secrete ACTH precursor levels in the range 139-18,000 pmol/l, which were significantly higher than patients with pituitary-dependent Cushing’s disease (9-104 pmol/l). Patients with carcinoid tumors also had ACTH precursor concentrations more than 100 pmol/l. Therefore using 100 pmol/l as the diagnostic cut-off has 97% percent sensitivity and 100% specificity [74]. A previous study using an assay for POMC alone, found good discrimination between ectopic and pituitary tumors. The levels of POMC in 19/19 patients with pituitary microadenomas were low, as opposed to being elevated in 16/20 patients with ectopic ACTH syndrome. The remaining four patients with ectopic tumors had undetectable levels of POMC and were later found to have bronchial carcinoid tumors [75]. This suggests that some carcinoid tumors are capable of processing POMC to ACTH. It is also suggested that further processing may occur since a C-terminal fragment of ACTH, termed corticotrophin-like intermediate lobe peptide (CLIP) has been detected in three bronchial carcinoid tumor extracts but were not found to be present in the peripheral circulation [76].

Some lab tests and biochemical markers help to differentiate between ectopic ACTH syndrome and Cushing’s disease. These include hypokalemia and some tumor markers [72-73]. Hypokalemia was reported in 42-70% of patients with ectopic ACTH syndrome [56-60]. Tumor markers may be elevated with neuroendocrine tumors [60,77,78]. Calcitonin, for example, was noted to be lower in patients with Cushing’s disease as compared to patients with ectopic ACTH syndrome, where it was found to be increased in 75% of patients with overt tumors and in 38% patients with occult tumors [60,78,79]. Other useful tumor markers include gastrin, glucagon, pancreatic polypeptide and others, where at least one of these tumor markers is found to be increased in 72% of patients with EAS [72,77-79].

Treatment: Surgical excision of the primary lesion is the best treatment of all ectopic ACTH syndromes. In such cases complete remission can be achieved in up to 83% of patients. It may also be useful to do multiple surgical excisions in cases of multiple recurrences [56-58,80]. Adrenalectomy (unilateral or radical) remains an option if hypercortisolism cannot be controlled by medical therapy and if the tumor secreting ectopic ACTH cannot be resected in the first place [57,60]. Adrenal blocking drugs via inhibition of steroidogenic enzymes are an effective medical treatment for patients with ectopic Cushion syndrome who are not amenable to surgical therapy or for those awaiting surgery to be done. Ketoconazole and metyrapone are the most frequently used drugs but their use may be limited due to their side effects like hepatotoxicity, seen with ketoconazole therapy, and the increased androgen and mineralocorticoid production noted with metyrapone [80]. Moreover appropriate medical therapy in small cell lung cancer is necessary for the immediate correction of hypercortisolism in order to minimize the side effect of myelosuppressive cytotoxic chemotherapy [79-80]. Etomidate infusions have been successfully used when rapid control of hypercortisolaemia in severely-ill patients with EAS [81]. Because tumors secreting ectopic ACTH may exhibit dopamine receptors or somatostatin receptors, somatostatin analogues or dopamine agonists were occasionally used either alone or as add on therapy to inhibitors of steroid synthesis in patients with incomplete resection and in those with recurrences [82,83]. In carcinoids causing ectopic ACTH syndrome external radiotherapy can also be utilized [78].

Prognosis: The predictors of the prognosis of ectopic ACTH syndromes include tumor histology and the severity of signs and symptoms of hypercortisolism, which were found to be associated to increased morbidity and mortality. This was mainly due to infections, peritonitis, increased risk of pulmonary embolism and heart failure. Bronchial carcinoids tend to have a good prognosis while small cell lung cancer and thymic carcinoids are noted for their bad prognosis [77-78].

Syndrome of inappropriate ADH secretion (SIADH)

Historical perspective: The first clinical case of a patient with SIADH was presented by Schwartz et al. [84] in 1957, when he described two patients with lung cancer who developed hyponatremia associated with continued urinary sodium loss. They postulated that the tumors led to the inappropriate release of antidiuretic hormone (ADH), later discovered to consist of AVP [84-85]. This was later confirmed since immunoactive AVP has been noted to be elevated in the plasma of patients with
brachyogenic carcinoma and in patients with cancers of the digestive tract [85-86].

Prevalence, Presentation and Diagnosis: About 14% of hyponatremia cases found in admitted patients is attributed to an underlying tumor. It usually accompanies but can precede the diagnosis of the tumor with an incidence of about 3.7% to 5% [86]. Syndrome of inappropriate ADH secretion is the most common cause of hyponatremia in this population. ADH is synthesized in the hypothalamus and transported down the pituitary stalk to the posterior pituitary, where it is stored. ADH binds to V2 receptors on the cells lining the collecting tubules in the kidney facilitating water reabsorption in the renal medulla. Some tumors may actually demonstrate multiple hormone production such as ectopic secretion of adrenocorticotropic hormone and ADH [87]. Ectopic secretion of ADH has been associated with small cell lung cancer, bronchogenic carcinoma, duodenal tumors, pancreatic tumors, thymus tumors, olfactory neuroblastoma, sarcoma, malignant histiocytosis, mesothelioma as well as other occult tumors [87-90].

The signs and symptoms of SIADH depend on the both the degree of hyponatremia and the rate at which it develops. A serum sodium concentration less than 120 mEq/L or serum osmolality less than 240 mOsm/kg is considered serious, irrespective of the rate of decline and patients can experience cerebral edema, permanent brain damage, brainstem herniation, or death [89].

The key points in diagnosing SIADH are the findings of a plasma osmolality less than 280 mosmol/kg, hyponatremia with a plasma sodium concentration of less than 134 mmol/l, hypotonicity, inappropriate increased urinary concentration with a urine osmolality of more than 100 mosmol/kg, and an elevated urine sodium concentration of more than 40 mmol/l. However it is important to note that a low urine sodium concentration does not exclude the diagnosis. Patients with SIADH are clinically euvolemic. Hypouricemia occasionally may be associated with SIADH as a result of increased excretion of nitrogen waste and plasma dilution [90].

SIADH is usually one of the most common causes of euvolemic hyponatremia. However other causes of euvolemic hyponatremia in these patients include inappropriate hypotonic fluid replacement, particularly following surgeries or diarrheal illnesses [91-95]. ACTH deficiency needs to be ruled out as well, since cortisol is necessary for the efficient excretion of free water, and glucocorticoid deficiency is usually associated with the retention of free water and thus hyponatremia leading to a picture identical to SIADH. These patients often have as well elevated plasma arginine vasopressin (AVP) concentrations, which contributes further to the tubular reabsorption of water [96].

Treatment: Fluid restriction and occasionally furosemide with salt supplementation are the recommended adjunctive therapy for severe hyponatremia. However the best treatment is the removal of the underlying tumor, or at least reduction of tumor mass by surgery, chemotherapy, or radiotherapy. Treatment with demeclocycline (150 to 300 mg/d) inhibits the effects of vasopressin on the kidney and is the preferable long-term treatment [95-96]. Demeclocycline can be used to manage chronic hyponatremia in patients with SIADH. The vaptans constitute a new class of drugs developed mainly used for the treatment of the hypervolemic and euvolemic forms of hyponatremia. They act through interfering with the antidiuretic effect of the hormone by competitively binding to V (2) receptors in the kidney. They were also found to be helpful in the treatment of the syndrome of inappropriate antidiuretic hormone (SIADH), especially when it is chronic and/or minimally symptomatic [97]. Few studies studied the efficacy of vaptans in SIADH patients. They were of short duration however did show that they are efficacious in increasing serum sodium concentrations [98-100]. Recently, two controlled trials of conivaptan used in a limited number of patients with euvolemic hyponatraemia, mostly due to SIADH, showed that it is effective to increase free water clearance and to correct hyponatraemia [100-102].

Ectopic GHRH production

Historical perspective: The first evidence of the existence of ectopic growth hormone secretion came from an old clinical observation noted in the 1960. Back then, it was noted that rare cases of carcinoids, especially those involving the bronchial tree, were associated with acromegaly [103-104]. Then in 1976, it was documented that removal of a bronchial carcinoid did result in remission of the acute disease in two acromegalic patients. It was proposed that these tumors were actually producing a substance with growth hormone releasing ability [104]. Several other reports followed. Then in 1982 three different molecular forms of GHRH were isolated, from pancreatic endocrine tumors in patients who had features of acromegaly, the longest being GHRH 1-44 NH2. Two other shorter peptides were also sequenced from the tumor extract, and they were GHRH 1-40 OH and GHRH 1-37 NH2 [105-106]. In 1984 it was discovered that the main biological activity of GHRH lies in its first 29 amino acids [107]. It was also found, that those GHRH which were extracted from tumor tissue, had the same amino acid sequence as the GHRH produced by the hypothalamus [108]. GHRH acts through binding to its receptor on somatotroph cells, hence activating adenylate cyclase resulting in an increase in intracellular cyclic AMP. Acromegaly results from an increase in IGF 1 secretion in peripheral tissues resulting from excessive secretion of GHRH [109-110].

Prevalence, presentation and diagnosis: Ectopic growth hormone releasing hormone producing tumor account for 0.5-1% of all acromegaly patients [109-110]. Many cases of ectopic GHRH were reported over the past 25 years. To prove the ectopic secretion of GHRH two criteria are needed. There must be a clear demonstration that this GHRH is actually produced by the tumor itself and the neoplastic cells from the tumor extract should stain positive for GHRH. The available GHRH radioimmunoassay enables the quantification of the amount of GHRH produced by the tumor. GHRH in peripheral blood is very high in patients with ectopic GHRH producing tumors as opposed to being normal or low in pituitary tumor secreting growth hormone. Although
plasma GHRH higher than 300 ng/liter is usually reported in patients with ectopic GHRH, however three cases of acromegaly due to ectopic secretion of GHRH have been reported with plasma GHRH between 100 and 300 ng/liter [109]. The decrease in GHRH level upon tumor resection would further prove ectopic GHRH secretion however in many cases metastasis is present at the time of the diagnosis and surgery would not be a valid option [108-109]. From the registry of the sole laboratory in France which measures plasma GHRH assays, 21 patients with ectopic GHRH secretion presenting with acromegaly were identified between 1983 and 2008. Their age ranged between 14–77 years and their median GHRH at diagnosis was found to be 548 (range 270–9779) ng/liter [110]. Two third of the tumors associated with ectopic GHRH production were carcinoids, especially of the lung and the gastrointestinal tract. Other reported tumors associated with ectopic GHRH secretion include pheochromocytoma [111] and lung cystic adenoma [112]. Among the lung carcinoids secreting GHRH, 78% were found to be located on the right side of the lung and the reason behind this observation is still unclear. In 35% of cases it was found that those lung carcinoids would have metastasis to the lymph nodes, liver and bones [113]. Carcinoids arising from the gastrointestinal tract were mainly found in duodenum and jejunum. Pancreatic endocrine tumors were the second most common cause of ectopic GHRH production arising from the tail of the pancreas and these tumors are not normally aggressive in nature [114-115]. Not all patients exhibit the acromegalic feature despite the fact that 30-60% of tumor cells of pancreatic endocrine tumors stained positive for GHRH. Moreover, there was no association between tumor size and acromegalic features.

However, in the France registry of patients with ectopic GHRH the primary neuroendocrine tumor was identified in 20 of 21 patients, 12 being pancreatic, seven bronchial and one appendicular. In these patients tumors were found to be large in size ranging between 10-80 mm, was identified using computed tomography scan in 18 of those patients and by endoscopic ultrasound and somatostatin receptor scintigraphy in the remaining two patients. In this study it was found that somatostatin receptor scintigraphy had a similar sensitivity to computed tomography scan (81 vs. 86%) Tumors were all well differentiated but 47.6% had metastasis at the time of diagnosis. 91 percent of those patients had their tumor completely removed and were considered to be in remission. The remaining patients were treated with somatostatin analogs. No correlations were found between GHRH levels and the tumor site or size or the presence or absence of metastases. Identification of increased plasma GHRH during the follow-up period was very highly predictive of recurrence [110].

The duration of symptoms before the diagnosis was made was found to be similar between ectopic producing GHRH tumors and GH secreting pituitary adenomas. The indolent course of bronchial carcinoids led to delay in the diagnosis of patients with a mean of 10.6 years as opposed to pancreatic endocrine tumors, where the mean duration for the diagnosis was around five years [108-109]. The classic manifestations of patients with ectopic GHRH producing tumors were found to be similar to those found in GH secreting pituitary adenomas. Ectopic co-secretion of ACTH was found in two of the reported cases of ectopic GHRH secretion by tumor [114]. Coexistent hyperparathyroidism was found in six of the reported cases. (115) High prolactin was found to be common in patients with ectopic GHRH production [116].

**Treatment:** Surgical removal of the tumor producing this ectopic hormone is the mainstay of therapy especially when no metastasis is detected with the resolution of acromegaly being evident with the first weeks of therapy [117-118]. Systemic therapy is necessary in patients with metastatic or inoperable disease and this includes chemotherapy and somatostatin analogues [119-120].

**Ectopic Prolactin (PRL) Production by Tumors**

**Historical Perspective:** First suggestion of ectopic production of PRL was by Rees et al. [115] in 1974, where a bronchial tumor was found to be actually producing the PRL hormone. Later, in 1986, a case of long standing gynecomastia associated with a hypernephroma, was reported in literature where serum PRL returned to normal after radical nephrectomy and remained so for 4 years without evidence of tumor recurrence [119].

**Prevalence, Presentation and Diagnosis:** Prolactin was found to be ectopically produced by several cancers including malignant tumours of the lung, kidney, ovary, breast and colorectal cancer [115,119-125].

There have been several reports recording high incidence of abnormal serum PRL in patients with uterine cervical carcinoma (around 30.8%). It was even found that during early stages of cancer, the degree and incidence of elevation in serum PRL levels were much greater than those found for carcinoembryonic antigen (CEA), which is generally considered to be a circulating cervical tumor marker [120]. These studies suggested that PRL may be a potential marker for detecting early occult tumors and could be a guide for therapy of cervical carcinoma [121].

Another documentation of ectopic PRL secretion came from a prospective study, including 46 female patients with a confirmed diagnosis of breast cancer, who were followed up for a total of 5 years, where serum concentrations of prolactin were measured before and after the therapy at regular intervals during the observation period. Their PRL concentrations were compared to those of 40 healthy women and 33 women with other types of cancer (mostly colorectal and lung cancers), who served as control groups. It was found that baseline serum concentrations of PRL were higher in breast cancer patients than in healthy women (16.9 ng/ml vs 12.2 ng/ml), and it was even higher when compared to patients with other cancers (18.3 ng/ml vs 13.3 ng/ ml). Moreover, metastases developed in all patients with high PRL levels and in only a third of patients who had normal PRL levels. The average time interval to metastasis was significantly shorter in patients with higher serum concentrations of PRL as compared to those with very low levels (5.4 ± 6.1 months). In addition, in patients with metastatic breast cancer, high PRL levels before treatment correlated with the size of metastases [122].

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A study was done by Bhatavdekar et al. [123] to assess the role of PRL in patients with Dukes B and C colorectal carcinoma. It found that preoperative PRL and CEA were significantly higher in patients with colorectal carcinoma as compared to controls. Moreover, prolactin was the most significant independent prognostic factor influencing overall survival. A significantly higher incidence of increased PRL levels were found in tumors of patients with Dukes B and C disease and those with Dukes C had even more increased PRL when compared to patients with Dukes B. This suggested de novo synthesis of PRL by tumor cells [123]. This was even demonstrated by the presence of PRL m RNA expression in 88% of colorectal carcinoma patients. The carcinomas secreting PRL were shown to have a growth advantage and hence a worse prognosis. In view of its prognostic value the authors suggested that this may provide insights into the treatment of colorectal carcinoma [124]. In a cross sectional study of 47 patients and 51 age and sex matched controls, serum PRL and CEA concentrations were assayed preoperatively using immunoradiometric assay kits. The study concluded that PRL may be a better tumor marker than CEA in patients with colorectal malignancy. Conversely, Baert et al. [125] did not find preoperative high PRL levels in a series of 32 patients with colorectal cancer. Furthermore, Indinnimeo et al. [126] found no hyperprolactinemia and/or PRL positive immunostaining in 30 patients with colorectal cancer and they suggested that PRL levels could not be used as prognostic marker in patients with colon cancer. Therefore, future prospective studies are needed to better understand the role of PRL as a prognostic factor in colorectal cancer.

Other Ectopic Hormone Syndromes

Tumor-Induced Osteomalacia: A clinical syndrome, also known as oncogenic osteomalacia, characterized by the over production of fibroblast growth factor-23 by certain tumors including mesenchymal tumors (osteoblastomas, giant cell osteosarcomas, hemangiopericytomas, hemangiomatos, nonossifying fibromas), resulting in the triad of phosphaturia, hypophosphatemia, and low serum levels of 1,25-dihydroxy vitamin D with osteomalacia and moderate to severe proximal myopathy. It clinically mimics X-linked or autosomal dominant hereditary hypophosphatemic rickets. Approximately 100 cases of tumor-induced osteomalacia have been reported [129-130]. Patients affected are usually adults over the age of 30, with a male-to-female ratio of 1.2:1. Diagnosis is very challenging. Laboratory and radiologic testing are essential for the diagnosis. Bone and indium-111 octreotide imaging are additional important diagnostic radiologic tools for small tumors not detected on routine physical examination or radiography [127-130]. Oral or intravenous supplementation of phosphate combined with vitamin D therapy is generally recommended in addition to the complete surgical removal of the tumor [131-132].

Rare ectopic secreting tumors: Polycythemia resulting from ectopic erythropoietin production is a rare clinical syndrome. Other less well-defined syndromes include production of thrombopoietin, leukopoietin, or colony-stimulating factor by certain types of tumors. These rare clinical syndromes have been usually identified in cerebellar hemangioblastoma, uterine fibroids, and pheochromocytomas, ovarian and hepatic cancers. Treatment includes surgery, chemotherapy or phlebotomy [133].

Conclusion

Paraneoplastic endocrine syndrome results from the ectopic production of hormones by different tumors. It is important to recognize this entity because it may lead to devastating clinical syndrome and may be the presentation of different tumors. In addition it significantly affects the prognosis of different tumor types. Important management of the original tumor including surgical resection or systemic therapy for inoperable disease is the mainstay of therapy.

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