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REVIEW

Endocrine Paraneoplastic Syndromes with Special Reference to the Elderly

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Introduction

In general terms, paraneoplastic syndromes may be defined as a combination of effects that occur far from the original site of the neoplasm or of its metastases. Their prevalence is 15% of malignancies *(1)*, mostly involving the lungs, stomach, and breast. Sometimes paraneoplastic syndromes may be more severe than the on-site effects of the tumor. They may anticipate, parallel, or follow clinical manifestations of the primary disease, as well as behave unpredictably. It is critical to recognize a paraneoplastic syndrome for the following reasons:

1. It may lead to the diagnosis of an underlying, previously unsuspected neoplasm.
2. It may dominate the clinical picture and therefore be misleading in terms of tumor origin and type.
3. It may follow the clinical course of the underlying disease and thus become very useful to monitor.

Paraneoplastic syndromes may involve any organ or system: however, the most common are the endocrine, neurological, dermatological, and hematological syndromes.

There are many metabolic consequences owing to neoplasms in old age. Some of them are brought about by the mechanical effects of an underlying tumor—for example, cachexia due to gastroenteric stenotic lesions, obstructive kidney disease, or metastatic liver failure. Sometimes the metabolic and endocrine syndromes occurring in the presence of tumors depend directly on the secretion of cytokines, peptide hormones, or precursors *(2)*. The latter condition, known as paraneoplastic endocrine syndromes (PNESs), is the subject of this article.

General Features of PNESs

PNESs depend on the secretion of hormones or hormone-like substances by nonendocrine tumors. Small amounts of such substances, mostly peptides, are also produced by normal nonendocrine tissues, acting on site as paracrine signals or cytokines. According to Odell's *(3,4)* hypothesis, neoplastic transformation may significantly amplify those signals, thus allowing the peptides to enter into circulation and act as hormones on target tissues. For this reason, the term *ectopic* is not accurate, and, currently, in the case of paraneoplastic hormone production, *inappropriate secretion* is preferred.

To ensure that a certain PNES is caused by a well-defined neoplasm, one or more of the following criteria must be satisfied (*5,6*):

1. There must be clinical or biochemical evidence of an endocrine abnormality in a neoplastic patient. Such evidence would suggest that the tumor is the source of hormone production; however, a second criterion must also be present.
2. Tumor removal causes the endocrine syndrome to disappear.
3. Hormone levels remain elevated after the typically involved endocrine gland has been removed.
4. A high arterovenous gradient is present across the tumor. This characteristic is not easily indicated, owing to both practical reasons and unpredictable hormone secretion by the tumor.
5. Higher hormone concentrations are found in the tumor than in the surrounding tissues.
6. Cultured tumor cells synthesize the hormone and/or hormone-specific mRNA is extracted from the neoplastic tissue. Again, this is only a suggestive criterion, because normal tissues are capable of producing hormones, such as proopiomelanocortin (POMC).

During old age clinical evidence of PNES may be very poor, as is the case with many other diseases in the elderly. Therefore, the clinical and biochemical patterns may be atypical, so that missing or incorrect diagnosis occurs more frequently compared to diagnosis in the young. On the other hand, because of the increased prevalence of some cancers typically associated with PNES, it is conceivable that the actual prevalence of PNES is much higher in the elderly than in the young. Unfortunately, to our knowledge, no sound epidemiological data have been published yet on this topic. The major PNESs are as follows *(7)*:

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1. Cushing syndrome
2. Hypercalcemic syndromes
3. Syndrome of inappropriate antidiuretic hormone (ADH) secretion or inappropriate antidiuresis (SIADH or SIAD)
4. Gynecomastia or other manifestations of hypersecretion of human chorionic gonadotropin (hCG), human placental lactogen (hPL), or other gonadotropins
5. Extrapituitary acromegaly
6. Hyperthyroidism owing to thyrotropin (thyroid-stimulating hormone [TSH]) hypersecretion
7. Hypoglycemic syndromes
8. Syndromes owing to hyperproduction of renin, erythropoietin and so on.

These syndromes are described in depth in the following sections.

Cushing Syndrome

The association between Cushing syndrome and various cancers was first described by Brown *(8)* in 1928 and later elaborated and characterized by Meador et al. *(9)* and Liddle et al. *(10)*. This PNES generally depends on a tumor-producing adrenocorticotropic hormone (ACTH) and/or corticotropin-releasing hormone (CRH) and, according to the analyses of different reports, seems to account for 10–20% of the total cases of Cushing syndrome *(11–13)*.

High amounts of biologically acting ACTH are generally found in the tumor tissue, yet immunoreactive ACTH is sometimes present in high concentrations in tumor extracts from patients without clinical manifestations of Cushing syndrome *(14,15)*. ACTH is most often present under its high-molecular-weight form, "big-ACTH," which is easily converted into the active ACTH by trypsin incubation *(15–17)*. Actually, ACTH-like immunoreactivity has been found in normal tissues. Moreover, other studies *(18–20)* led to the isolation of a high-molecular-weight glycoprotein considered to be POMC, i.e., the biologically inactive, trypsin-sensitive precursor of β-endorphin and ACTH. Thus, all tissues are able to secrete small amounts of POMC-related peptides, probably endowed with autocrine or paracrine functions. The majority of cancers, therefore, secrete larger amounts of the same peptides into the blood. This particular PNES is then characterized by POMC hyperexpression and abnormal posttranslational processing, with consequent release of ACTH and/or its precursors, which, because of their enormous concentrations, are able to induce hypercortisolism *(21)*.

The tumors most often associated with Cushing syndrome are those affecting the lungs, thymus, pancreas, thyroid medullary carcinomas, pheochromocytomas, paragangliomas, and neuroblastomas. The cases related to liver, prostate, and breast carcinoma are by far less frequent. No cases originating from tumors of mesodermal origin have been reported yet. Fortunately, unlike early views *(10,22,23)*, the kind of tumor most often involved in the genesis of this PNES is of a benign nature *(6)*, and is represented especially by carcinoids *(11,24–27)*. Among these, bronchial carcinoid accounts for 36–46% of the cases, whereas small-cell lung carcinoma (SCLC), which has been considered the major cause for a long time, is only associated with 8–20% of cases. Actually, about 30% of SCLCs hypersecrete ACTH, but only a few have proper clinical expression *(28)*. Diagnostic underestimation *(6)* may eventually be explained because an endocrine syndrome is underestimated and therefore not even reported when present in a patient with a poor prognosis lung cancer. By contrast, it is easier to find reports in the literature concerning occult neoplasms associated with ACTH hypersecretion *(28–30)*. This is typically the case of bronchial carcinoids, which often are hidden while symptoms undistinguishable from those of a typical pituitary-dependent Cushing syndrome continue for years *(11,27,28)*.

Clinical features reflect the differences between typical pituitary and extrapituitary ACTH hypersecretion. The fast-occurring lethal consequences of the originating neoplasm often prevent a series of symptoms from becoming evident. Proximal muscle weakness, weight loss rather than weight gain, slight changes in body fat distribution, hypertension, and melanodermia were mainly reported in earlier cases *(10)*. Moreover, the enormous increase in cortisol levels caused mineraloactive effects such as hypokalemic edema associated with high or normal circulating sodium levels. This is even more evident for elderly patients, who mostly show hypokalemic alkalosis in association with weight loss, impaired glucose tolerance, and a tumor mass.

When this PNES occurs in patients hosting a slow-growing neoplasm, clinical manifestations may totally resemble those of typical Cushing syndrome of pituitary origin, and in the elderly, the diagnosis may be especially difficult to make. Some biochemical changes may suggest the diagnosis of PNES, including very high cortisol and ACTH levels (which are not suppressed by dexamethasone), strong mineraloactive effects, and negative response to ovine CRH (oCRH). In cases in which diagnosis is difficult, the only test to be used is inferior petrous sinus catheterization associated with blood drawn before and after the ACTH/cortisol stimulation with oCRH + desmopressin (DDAVP) *(31–33)*.

In addition to the usual imaging techniques, currently it is recommended that a scintigraphic scan using somatostatin receptor analogs according to the technique proposed by Lamberts et al. be performed *(34)*. In the case of tumors that are able to uptake the labeled marker, this technique has clear-cut advantages not only for diagnostic purposes, but also for the subsequent treatment with octreotide. In fact, this drug seems to enhance the effects of associated treatments, thus making the PNES less and less severe *(35,36)*.

Once the paraneoplastic Cushing syndrome has been diagnosed, circulating tumor markers may help the localization of the tumor itself and the follow-up during treatment. The cosecretion of tumor markers and ACTH in this kind of PNES may have a prevalence as high as 62–70% of cases. The most common are calcitonin, catecholamines, intestinal peptides, 5-hydroxyindole acetic acid, neuron-specific enolase, alpha fetal protein, carcinoembryonic antigen, chromogranins, and β-hCG.

Obviously, the best treatment for paraneoplastic Cushing syndrome is surgical removal of the underlying tumor, although health prospects differ depending on the kind of neoplasm. Full recovery is expected in the case of benign tumors, such as bronchial carcinoids or pheochromocytomas. No relapse is expected for a number of years after careful removal of slowly progressing malignancies such as pancreatic islet tumors or neoplasms producing only localized lymph node metastases, such as medullary thyroid carcinoma.

High-malignancy neoplasms, such as SCLC, behave differently, so that only a combination of surgery, multiple chemotherapeutic agents, and radiotherapy may grant some short-term benefit. In such cases the presence of Cushing syndrome is an independent unfavorable prognostic factor; therefore, it is crucial to start with its treatment before giving chemotherapy *(28)*.

When the PNES persists and is still severe and disabling, despite the apparently effective treatment of the underlying tumor, it is appropriate to administer drugs in order to limit its manifestation by ACTH inhibitors or cortisol inhibitors.

ACTH Inhibitors

The presence of somatostatin (analog) receptors in many ACTH- or CRH-producing tumors may be used not only for the detection of tumor by radiolabeled octreotide but also for its treatment. In fact, octreotide can inhibit tumor cell growth, and this effect is proportional to the number of somatostatin receptors on the cell surface and to circulating chromogranin A levels *(37–39)*. Despite the patient's improving clinical condition, long-term effects tend to be less than initially expected, especially in terms of tumor growth rate.

Cortisol Inhibitors

Currently, bilateral adrenalectomy is life-threatening itself and, therefore, considered the last possible treatment and is performed only in severe treatment-resistant cases. The same considerations hold true for adrenal artery embolization, to be performed when surgery is not possible. Nevertheless, when it is absolutely necessary, inhibitors of adrenal hormone biosynthesis, such as aminogluthetimide, methirapone, ketoconazole, mytotane (op'-DDD), or competitive inhibitors such as RU486 *(40,41)*, are used.

Hypercalcemic Syndromes

The association between hypercalcemia and cancer was first described by Zondek et al. *(42)* in 1924, but only in 1941 did Albright *(43)* suggest a cause-effect relationship between the two, and hypothesize that the tumor produces a parathyroid hormone (PTH)-like substance. Actually, the hypercalcemic syndrome is one of the most prevalent PNESs. Yet, neoplasms themselves are the first cause of hypercalcemia in hospitalized patients and the second in the general population *(1),* because bone destruction by metastases directly increases circulating calcium levels, thus strongly contributing to specific statistics. Nevertheless, the latter condition does not represent a PNES and is not discussed herein. Instead we focus on circulating hormone- or hormone-like-dependent hypercalcemic syndromes caused by solid tumors and on-site neoplastic osteoclast-mediated osteolytic effects *(44)*.

Solid Tumors

Solid tumors most often involved in hypercalcemic syndromes are breast carcinoma; squamous cell lung carcinoma; and kidney, esophagus, ovary, head, and neck carcinomas *(45)*.

In the 1960s, PTH was thought to be the main underlying source of hormone hyperproduction. We now know that PTH-related peptide (PTHrP) is often responsible for this PNES. PTHrP differs from PTH due to some amino acid sequences, especially those pertaining to the C-terminal portion *(46)*. Conversely, it is quite similar to PTH at the level of the NH_2-terminal end, allowing it to bind easily to PTH receptor, thus triggering cyclic adenosine monophosphate (cAMP) production and bone resorption (*47–50*). PTHrP synthesis seems to be controlled by a separate gene with respect to the one devoted to PTH synthesis. These genes are located on chromosomes 11 and 12 and are thought to be the result of a duplication of a common ancestral gene occurring very early in the phylogenetic event series *(51)*.

This PNES differs from typical primary hyperparathyroidism (PHP) in that bone resorption is generally more evident, whereas bone formation is much slower, and circulating calcium levels decrease after biphosphonates. Moreover, neither hyperphosphatemia nor hyperchloric acidosis occur (which is quite usual in PHP), slight metabolic alkalosis may be found, and $1,25(OH)_2$-vitamin D_3 circulating levels (typically increasing in PHP) are often lowered *(52,53)*. A diagnostic clue is obtained from circulating PTHrP assay, showing very high levels in this PNES and very low levels in healthy individuals or in those suffering from PHP.

Some investigators *(54,55)* reported that PTHrP and/or cAMP were undetectable in some patients suffering from nonmetastatic solid tumors associated with hypercalcemia. In fact, other circulating factors produced by neoplasms

can positively interact with PTHrP, thus causing different clinical manifestations of the hypercalcemic syndrome by either synergistically acting on some cells or antagonizing its effects in other cells. For instance, some cytokines, such as granulocyte colony-stimulating factor and interleukin-1 (IL-1), when associated with high PTHrP levels, may also cause cachexia and leukocytosis *(56)*. Other peptides, such as transforming growth factor-α (TGF-α), prostaglandin E_2 (PGE_2), and tumor necrosis factor (TNF), have also often been identified in and isolated from sera obtained from neoplastic patients.

On-Site Neoplastic Osteoclast-Mediated Osteolytic Effects

On-site neoplastic osteoclast-mediated osteolytic effects occur most often in the presence of hematological neoplastic diseases, such as multiple myeloma and lymphomas; breast carcinoma is also involved in the genesis of such PNESs. We do not yet know the structure of the involved peptides, and refer to all of them as osteoclast-activating factors (OAFs). In multiple myeloma, the OAF seems to be TNF-β (also termed *lymphotoxin*; *[57]*). PGE_2 is considered to be an OAF in the case of breast carcinoma, and in the case of other tumors, different cytokines have been reported to be implicated in the genesis of the syndrome, such as IL-1, IL-6, TNF-α, and TGF-β.

Interestingly, according to some publications *(58–62)*, these tumors are able to hydroxylate 25-OH-vitamin D_3 to 1,25$(OH)_2$-vitamin D_3 as would a normal kidney in a healthy individual; and, conversely, kidney carcinomas would be associated with normal to low circulating 1,25$(OH)_2$-vitamin D_3 levels *(53,54)*.

The ideal treatment would be the complete removal of the underlying tumor, but sometimes the effects of hypercalcemia have to be eliminated first. Thus, a palliative treatment may be given, aimed at both hypercalcemia *per se* and its life-threatening clinical manifestations, based on calcium levels and severe neurological or gastroenteric symptoms often occurring when calcium concentrations exceed 0.4 m*M*/L. The therapeutic goal is a gradual decrease in calcium ion circulating levels, i.e., their normalization within days (never try to obtain normal calcium levels within hours!) in order to avoid potentially lethal intracellular electrolyte derangement. Rehydration is needed by the iv route together with a hypocalcemic agent. Preference should be given to furosemide associated with isotonic saline infusion *(63–65)*. Other possible treatments are the use of glucocorticoids (the efficacy of which is still debated), mitramycin (quite effective, yet potentially hepatotoxic and nephrotoxic, and therefore is used in low dosage, in association protocols), and calcitonin (currently considered not to be ineffective) *(65–67)*. Because bone resorption is the main reason for this PNES, therapeutic attention is focused mostly on its inhibitors. Biphosphonates are mostly used among the latter, because they are effective and free of major side effects *(68–70)*, although hypercalcemia owing to epithelium-derived neoplasms seems to be relatively resistant to them. Gallium nitrate is able to lower calcium levels in either the presence or absence of metastases as well as in epithelium-derived tumors (*71–73*). Currently, the use of a specific PTH receptor is being investigated.

Inappropriate Antidiuresis Syndrome

SIAD is mostly due to ADH hypersecretion by tumor cells. Still, in some cases, hyponatremia is not due to ADH but to other substances, such as atrial natriuretic peptide produced by the neoplasm *(74)*; thus, SIAD is currently preferred to the previously used SIADH *(75)*.

SIAD depends on the presence of a SCLC in 60% of cases *(76)*, although other lung carcinomas may be involved *(77,78)*, as well as gastrointestinal neoplasms, lymphomas and prostate, bladder, or uterus (cervix) carcinomas *(79–85)*. Its prevalence is probably much greater than expected from official reports. In fact, the underlying tumors are generally very aggressive and lead to fatal complications even before SIAD is hypothesized. Moreover, its leading symptom, hyponatremia, is extremely frequent, especially in hospitalized elderly patients and therefore often overlooked. Another reason that many SIAD cases may be misdiagnosed is that its symptoms are often subtle and misleading (e.g., sodium levels may be at the lower reference limit for some time) so that they are considered as part of the geriatric picture itself.

SIAD may even anticipate the diagnosis of SCLC many months before, but it does not make the SCLC prognosis more severe. In about two of three cases, SIAD has the same clinical course as the underlying tumor. This makes its recognition and follow-up extremely useful *(1)*.

Diagnosis of SIAD is made when hyponatremia associated with plasma hypoosmolality and inappropriately concentrated urine is present in a euvolemic patient. In fact, the conditions to exclude before hypothesizing a SIAD are volume depletion; edema; and functional abnormalities of the kidneys, adrenal glands, or thyroid *(2,86)*. ADH levels are inappropriately high in the classical SIADH and are not suppressed by plasma hypoosmolality. In SIAD, sodium balance is maintained and water ingestion prompts natriuresis, whereas in volume depletion or edema hyponatremia is associated with sodium retention *(87)*. Even under baseline conditions, continuous renal sodium excretion often occurs. In these cases, low circulating blood urea nitrogen and urate levels rule out the possibility of kidney hypoperfusion as the underlying disease. It must be stressed, however, that hyponatremia is not always present in SIAD patients, especially in the elderly, because of the reduction in water intake *(88)*. Clinical manifestations may be subtle or absent for a long time if water intake is low, and it is only when hyponatremia becomes severe that the symptoms for water intoxication appear (i.e., anorexia, nausea,

vomiting, headache, asthenia, confusion, and pseudobulbar palsy), with the outcome of coma and death.

As with all PNESs, the best treatment is the removal of the underlying tumor, or at least reduction of tumor mass by surgery, chemotherapy, or radiotherapy. Care should always be used with cyclophosphamide chemotherapy, because this drug may even cause SIAD when used in high dosages and in association with a large amount of water in order to prevent chemically induced hemorrhagic cystitis *(89)*.

Support treatment based on fluid balance monitoring is still the most relevant. Hyponatremia occurs only when the fluid intake is greater than water excretion. Therefore, 800 mL of fluid should be allowed daily, whatever its sodium content. With outpatients this does not appear to be feasible; therefore, the use of furosemide together with salt supplementation is preferred. In the case of saline infusion, Henle's loop diuretic agents must be used in order to prevent the paradoxical decrease of natremic levels caused by natriuresis uncoupled to diuresis *(90,91)*. Hypertonic saline is infused only in case of water intoxication and when circulating sodium levels are 100 meq/L, carefully avoiding rapid changes, which may cause pons myelinolysis. Eventually hypokalemia must be corrected and FANS must be avoided. In fact, the latter drugs enhance the antidiuretic effects of ADH by blocking the synthesis of PGE_2, which in turn inhibits ADH hydroosmotic properties *(75)*. Lithium is not currently used because its effects are not easily predictable and it has major adverse effects, whereas demeclocycline is still widely used, inducing ADH resistance *(92,93)*.

Gonadotropin Hypersecretion Syndromes

hCG is a placental glycoprotein mainly secreted by the trophoblast. An hCG-like molecule has also been found in gonadotropin-secreting pituitary cells *(94,95)*. It consists of two subunits: the α chain and the β chain. The α chain, species specific, has the same amino acid sequence as three other pituitary glycoprotein hormones: luteinizing hormone (LH), follicle-stimulating hormone, and TSH. The β chain differs from any other gonadotropin but is rather similar to the one from LH.

During the 1960s, extrapituitary gonadotropin secretion was thought to be rare, occurring mostly in trophoblast cells and in neoplasms of trophoblast origin *(96,97)*. Subsequently, many nonendocrine tumors and normal tissues were shown to produce hCG *(98,99)*. Based on investigations on the degree of hCG glycosylation, Odell *(3)* showed that hCG-like material may be virtually produced by all normal nonendocrine tissues, reinforcing the concept of "inappropriate" rather than "ectopic" secretion in PNES. Still, such material is almost biologically inactive in vivo, owing to poor glycosylation. It was hypothesized that all types of carcinoma synthesize this substance whereas only a few are able to add glucose residues to it. In fact, only highly glycosylated molecules are slowly degraded, so as to become detectable in plasma and biologically active.

Many cancers are associated with hCG hyperproduction *(100)* but only a few are most probably associated with this PNES. Hepatoblastoma may cause isosexual precocious puberty in young patients, and giant-cell lung carcinoma, gastric carcinoma, and kidney carcinoma may actually cause gynecomastia in the adult and elderly male *(101)*. Interestingly, when high amounts of hPL or hPL-like material are secreted by the neoplasm (as may occur in lung carcinomas), not only gynecomastia but also distal hypertrophic osteopathy becomes a very useful marker *(102)*.

Unfortunately, even though these signs easily address the early diagnosis of gonadotropin-mediated PNES, hCG assay is not as useful for the diagnosis and follow-up of nontrophoblastic tumors for the following reasons:

1. It is aspecific. Two to three percent of healthy individuals or patients bearing any kind of benign tumors show high levels of circulating hCG-like material *(103)*.
2. It has poor sensitivity. Many people with this PNES have low circulating hCG-like levels.
3. It has poor correlation to tumor stage, with the presence of metastases and with a degree of tumor differentiation.

Extrapituitary Acromegaly

Extrapituitary acromegaly may be the result of either growth hormone (GH) or GH-releasing hormone (GHRH) hypersecretion by extrahypothalamic and extrapituitary tumors. This is one of the most poorly documented PNESs. Immunoreactive GH has been found in extracts from lung adenocarcinomas and breast cancers, yet free of any clinical manifestations (acromegaly) *(104)*; on the other hand, many normal tissues contain GH molecules *(105)*. To our knowledge, only two cases have been reported in which GHRH production and GH hypersecretion occurred in the presence of acromegaly.

GHRH-secreting tumors causing acromegaly have been found relatively more often, in about 50 cases *(106)*, and GHRH production by nonendocrine tumors was even described before hypothalamic GHRH characterization. This peptide may also be found in many extrahypothalamic tissues and in various types of tumors (*107–108*). The most prevalent seems to be the bronchial carcinoid, followed by pancreatic tumors, lung microcytomas, and adrenal masses (*109–110*).

For diagnostic purposes, pituitary challenge and inhibition tests are not useful in terms of differentiating the PNES from the pituitary-dependent syndrome or from hypothalamic acromegaly, the latter being generally caused by hamartomas, gliomas, or gangliocytomas. The best diagnostic tools are currently represented by imaging techniques.

Hyperthyroid Syndromes

Because hyperthyroid syndromes have not been frequently reported, we describe them at the end of this article.

Still, they deserve our attention because their occurrence is more frequent in the elderly than in the young. They depend on massive neoplastic secretion of TSH by extrapituitary tissues. The tumors most often involved in the genesis of inappropriate TSH secretion originate from the gastroenteric system, the hematopoietic system, the breast, and the bronchial tissue. They seldom cause a typical hyperthyroid syndrome, as in the case of diffuse toxic goiter in the young. Because this PNES mostly affects the elderly, the patient generally only reports the combination of rapid heart rate and weight loss. During medical examination, only increased heart rate is usually found, because goiter has not had enough time to develop.

When circulating thyroid hormone assays are performed, extremely high levels of FT_3 and FT_4 are detected, together with high TSH levels. Once again, the treatment relies on surgical removal of the underlying tumor, but methimazole or propylthiouracil, together with propranolol or other β blockers are generally needed, at least in the beginning, to eliminate the life-threatening effects of muscle deterioration and high oxygen consumption in an elderly subject already suffering from a severe illness.

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