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Paraneoplastic Syndromes in Patients with Urological Malignancies

Key Words

Paraneoplastic syndrome • Ectopic hormonogenesis •
 Kidney • Prostate • Bladder • Urothelial carcinoma

Abstract

Introduction: Paraneoplastic syndromes (PNS) may represent the main clinical problem in cancer patients; however, the knowledge of their clinical aspect remains quite poor among urologists. **Objective:** To provide urologists with an overview on main clinical aspects of PNS that have been reported to be associated to urological cancers. **Methods:** Literature search of peer-reviewed papers published by July 2008. **Results:** All genitourinary tumors can cause a PNS, and renal cell carcinoma is the most frequent urological malignancy involved. Prostate cancer is the second urological tumor associated with PNS which, conversely, are uncommon in bladder cancer and rare in testicular cancer. Tumor neuroendocrine differentiation is involved in most endocrine PNS. Neurologic PNS are very uncommon but may dominate the clinical picture and need a high suspicion index to be recognized. Important advances have been made on radionuclide scan methods in order to detect the primary tumor. The most effective treatment strategy is always represented by the radical therapy of the underlying cancer, but specific therapeutic options are sometimes available. **Conclusions:** Endocrine PNS are frequently associated with urological cancers, especially renal and prostate carcinoma. PNS have been rarely reported in association with cancers of bladder, urethra and testicle.

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Introduction

Paraneoplastic syndromes (PNS) are defined as a collection of symptoms and clinical signs occurring in cancer patients and involving systemic effects taking place remotely from the tumor; they are not related either to its local repercussion or distant spread and are not caused by infection, nutritional deficiency or treatment.

A paraneoplastic phenomenon usually arises from (a) biologically active substances (hormones, hormone precursors, or hormone-like substances) aberrantly produced by the underlying neoplasm, (b) modulation of the immune system via autoimmunity, immune complexes production and immune suppression, (c) unknown causes.

To recognize a PNS may be clinically relevant for several reasons: (a) it can lead to the diagnosis of a previously undetected neoplasm; (b) it can dominate the clinical picture and thus lead to errors with respect to the origin and type of primary tumor; (c) it can follow the clinical course of the underlying tumor and thus be useful for monitoring its evolution (neoplastic marker).

An increasing number of reports on PNS can be found in the urological literature over the years, and this is partly explained by the availability of better diagnostic tools and more effective therapies that, by prolonging survival of cancer patients, may promote the occurrence of neoplastic hormonogenesis.

In urology, the following groups of PNS are of clinical interest because of their incidence:

- endocrine PNS (EPNS) caused by inappropriate release of hormonal peptides;
- PNS caused by inappropriate release of biologic amines;
- PNS caused by the inappropriate release of growth factors;
- renal cell carcinoma (RCC)-related PNS.

Furthermore, neurological PNS (NPNS) secondary to urological malignancies will be exposed synthetically because of their very low incidence.

Methods

A systematic literature search of peer-reviewed papers published by July 2008 was conducted. Medline databank was searched employing both 'MeSH' and 'free text' protocols and using the following search terms: 'prostate' or 'bladder' or 'testicular' or 'renal' or 'urologic' and 'cancer' and 'paraneoplastic syndrome'. A hand search of reference lists of retrieved relevant articles was also performed.

Endocrine PNS

The endocrine PNS (EPNS) are related to the aberrant hormonal production by tumors. The incidence of EPNS is underestimated because of subclinical hormonogenesis, low suspicion index or lack of multidisciplinary approach. Most EPNS are present in association with tumors of neuroendocrine phenotype, such as small cell carcinomas (SCC). Other syndromes, such as humoral hypercalcemia of malignancy (HHM), are associated primarily with squamous carcinomas of different primary sites.

The nature of tumor-produced hormones seems essentially indistinguishable from that of native hormones, although tumors frequently produce precursors or hormone fragments with less biological activity. In these instances, clinical syndromes related to hormone excess may be absent or muted despite the fact that levels of immunoreactive hormones are increased. Production of multiple hormones by a tumor is not uncommon.

Several molecular mechanisms have been described to explain the inappropriate release of hormonally active substances by tumors causing EPNS (table 1). Furthermore, iatrogenic selective pressure, such as biochemical castration in prostate cancer (PCa), might contribute to the induction of neuroendocrine phenotype causing PNS.

EPNS related to the inappropriate production of dimeric glycoprotein (FSH, LH, TSH, etc.), requiring more complex synthetic mechanisms, are less frequent than those related to polypeptidic hormones (parathyroid hormone-related peptide (PTHrP), antidiuretic hormone (ADH), adrenocorticotrophic hormone (ACTH)/pro-opiomelanocortin, etc.). Similarly, EPNS due to the production of steroid hormones are uncommon.

With regard to the diagnostic workup of the underlying tumors, important advances have been made in radionuclide scan methods (table 2). Ultrasound imaging, CT and MRI, can also help to identify the tumor and to obtain a biopsy. Imaging examination (e.g. SPECT) and laboratory tests (e.g. stimulatory and suppressive functional hormonal tests) allow ruling out hyperplastic-neoplastic primary diseases of endocrine glands.

Paraneoplastic Hypercalcemia

There are two major groups of malignancy-associated hypercalcemia: (1) HHM, related to the presence of circulating hormones, predominantly PTHrP and (2) localized osteolytic hypercalcemia, caused by paracrine factors, such as prostaglandins, secreted by the tumor cells. However, these categories represent a spectrum since in some cases of localized osteolytic hypercalcemia the mediator of hypercalcemia is PTHrP. In addition to PTHrP, other factors may play a major role including TGF- α , TL-1, IFN- β , lymphotoxins, PGE and 1,25-dihydroxy-cholecalciferol.

HHM is the most common EPNS and is present in up to 30% or more of all patients with hypercalcemia. PTHrP production leading to HHM is a well-described paraneoplastic phenomenon which may be seen in as many as 20% of patients with cancer, usually SCC of breast, lung, and genitourinary tract [1, 2].

Occasionally reported in association with bladder urothelial carcinoma (BCa) [3], HHM is the most common PNS among patients with RCC, affecting between 13 and 20% of patients [4]. However, nonparaneoplastic, bone metastasis-related hypercalcemia is also highly prevalent among RCC patients. Of those with hypercalcemia and RCC, approximately 75% have high-stage lesions and 50% bone metastasis [4, 5], although neither the presence nor degree of hypercalcemia has been shown to have a significant correlation with tumor grade or survival [6].

PTHrP is a polyhormone of the parathyroid hormone (PTH) family. Thus, a family of PTHrP peptides with diverse hormonal activities are generated by alternative splicing of the primary transcript. PTHrP peptides exert

Table 1. Pathophysiologic mechanisms advocated to explain the inappropriate release of hormonally active substances by tumors causing EPNS

Derepression hypothesis	Reactivation of biochemical pluripotency caused by genetic derepression in undifferentiated tumor cells. The regression of the oncotype to earliest differentiation phases would induce the genetic expression of transcriptional factors active in the early phases of embryogenesis. In this way, for instance, ASCL-1, achaete-scute complex (<i>Drosophila melanogaster</i>)-like-1, which during embryogenesis is normally suppressed by the differentiation-inducing factors HES-1 (hairy enhancer of split-1), is responsible of the neuroendocrine phenotype expression in the SCC ('oat cell carcinoma').
Neuroendocrine hypothesis	The higher incidence of ACTH and LPH production among amine-precursor uptake decarboxylation (APUD) tumors, not particularly undifferentiated, could be explained in two ways: (1) Neuroendocrine cells originating from the neural crest, normally present in many organs and usually quiescent in the postmitotic phase G0, may gain proliferative capacity (re-entry in the 'cell cycle') and clonal expansion until causing PNS; these cells may also constitute a tumor mass with only neuroendocrine oncotype (SCC and apudomas such as carcinoids). (2) Based on the stepwise, irreversible repression hypothesis of cellular differentiation, in APUD cells the gene for ACTH-LPH coding may be repressed at the terminal stage of differentiation and may, therefore, be very easily derepressed by neoplastic transformation; on the other hand, the ACTH-LPH gene may be repressed at a relatively early stage in non-APUD cells and be difficult to reactivate even after neoplastic transformation.
Oncogene hypothesis	Activation of specific oncogenes, in particular tumor cell populations. In this way, the activation of Kras-MAP (mitogen-activated proteins) kinase via a signaling cascade ('MAPK cascade'), until the nuclear expression of L-myc, leads to the production of PTHrP, CGrP and catocalcin in SCC. In RCC as well, the activation of the gene for PTHrP coding would be induced by epigenetic alterations leading to its hypo- or demethylation.
Hybridization hypothesis	Hybrid formation between epithelial tumor cells and neuroendocrine cells of APUD system, thus originating cells with mixed phenotype able to release hormonal substances.
'Prohibited contact' hypothesis	Release in the blood of substances normally produced and confined in the tissue when the tumor arises, with consequently systemic effect. This phenomenon may occur because of disrupted vascularization inside the neoplasm and surrounding tissue and because of interrupted basal membrane.

significant control over the proliferation, differentiation and death of many cell types. Binding to the same receptor (type I PTH receptor), PTHrP shares many cAMP-mediated actions with PTH leading to increased calcium release from bone (pro-osteoclastic activity), reduced renal calcium clearance and reduced renal phosphorus reabsorption.

The clinical picture of HHM can be very polymorphic with some patients showing aspecific symptoms such as asthenia, headache, lack of appetite, nausea, vomiting, constipation, polyuria-polydipsia (due to nephrogenic diabetes insipidus), and others exhibiting more severe and specific clinical presentation such as acute confusional or lethargic state or even coma associated with very high calcemia (>12 mg/dl). When calcemia exceeds 18 mg/dl, shock and death occur.

The usual laboratory pattern is elevated – total and ionized calcium in the absence of other causes (such as excessive vitamin D, sarcoid, bone metastasis), low levels of phosphorus and chlorus, low PTH (PTH may be over

the lowest value of the reference interval), high levels of phosphates and cAMP in the urine. Additionally, low levels of 1,25-(OH)₂-vitamin D₃ are seen due to renal inhibition of 1,25-hydroxylase. Measurement of PTHrP can be of assistance in an otherwise unexplained hypercalcemia.

Notably, patients affected by PCa with neuroendocrine pattern and expression of PTHrP frequently show normal calcemia or even hypocalcemia due to the so-called 'bone hunger syndrome', a well-recognized metabolic derangement of metastatic PCa patients. This syndrome is characterized by calcium entrapment in bone as a consequence of excessive osteoblastic activity leading to hyperparathyroidism in response to calcium demand; PTH elevation stimulates osteoclasts at sites distant from those involved by the tumor [7]. Furthermore, PTHrP in PCa patients may be cleaved and inactivated by the PSA [7].

Oncologically effective tumor treatments usually result in the resolution of the hypercalcemic syndrome. Ex-

Table 2. Diagnostic methods of nuclear medicine for the diagnostic workup in patients with EPNS

Somatostatin receptor scintigraphy (SRS or octreotide scan)	A type of radionuclide scan used to find carcinoids and other types of tumors and their metastases, performed using somatostatin-like drugs: ^{111}In -octreotide-DTPA (DTPAOC or pentetreotide) or the more recent DOTA-d-Phe(1)-Tyr(3)-octreotide which, labeled with the beta-emitting radioisotope yttrium-90, has recently been used for the treatment of patients with advanced somatostatin receptor-positive tumors who had no other treatment option. Specific radioactive markers for neuroendocrine tumors (e.g. ^{111}In -DTPAOC) can be used as guide for surgery with therapeutic or diagnostic purpose (radio-guided surgery).
'Three-step' immunoscintigraphy	This method, by using monoclonal antibodies anti-chromogranin A biotinylated (first step), followed by the avidin (second step) and ^{111}In -biotin (third step), has become a diagnostic tool after the detection of chromogranin production in endocrine tumors. In fact, the ability to visualize tumors using immunoscintigraphy depends on the ratio of the specific accumulation of radiolabeled antibodies in the tumor (hot spot) to the aspecific accumulation of radiotracer in the surrounding tissues (background); in order to optimize this ratio, three-step immunoscintigraphy increases the amount of radioactivity tied to the tumor and decreases the aspecific capture of radiotracer.
Positron emission tomography (PET) with ^{11}C -5-OH-tryptophan or with ^{11}C -levoDOPA	It is based on the metabolic capacity of APUD cells to accumulate and decarboxylate these substances, precursors of serotonin (carcinoid) and dopamine (pheochromocytoma, neuroblastoma), respectively. It is now possible to combine in one device the functional-metabolic (PET) with morphologic (TC) imaging.

cept for very severe situation requiring urgent treatment, HHM does not always require pharmacologic treatment [8]. Physiological homeostatic mechanisms and volume repletion with normal saline can usually maintain calcium levels under safety limits. If necessary, drugs can be employed which inhibit osteoclasts and bone resorption (bisphosphonates), or favor calcium fixation in the bone (calcitonin). Promising results have come from phase 1 trials showing a potent inhibitory effect of osteoprotegerin or anti-PTHrP antibodies on osteoclasts differentiation/activation. In refractory cases, the chelant agent EDTA (ethylenediaminetetraacetic acid) or plicamycin (mithramycin), which decreases serum calcium concentrations by inhibiting RNA synthesis in osteoclasts, may be employed. For very high levels of calcemia the use of hemodialysis may be necessary.

Paraneoplastic Hypercortisolism

Different conditions of inappropriate neoplastic hormonogenesis can determine overproduction of glucocorticoids and/or mineralocorticoids from the adrenal gland causing paraneoplastic hypercortisolism (PNHC): (1) ectopic production of corticotropin-releasing hormone, or (2) ectopic production of pro-opiomelanocortin, a polypeptidic precursor ACTH able to directly produce stimulation and hyperplasia of the adrenal cortex.

The incidence of PNHC is reported with increasing frequency, reaching in recent series the 40% of all types of hyperadrenocorticism. The main causes are pulmonary SCC and, with decreasing frequency, carcinoids, PCa, RCC and SCC of prostate and bladder [9–13]. PNHC is a particularly pernicious complication of PCa as adrenal stimulation can produce testosterone levels within the normal range, despite medical or surgical castration [13].

Clinically, patients with PNHC may present clear signs and symptoms of Cushing's syndrome: rapid weight gain with central obesity, a round face, excess sweating, telangiectasia, red striae, proximal muscle weakness, osteoporosis, hyperpigmentation and lipodystrophy, persistent hypertension, insulin resistance and various psychological disturbances. Muscle weakness due to marked hypokalemia could be the first manifestation and can dominate the clinical picture [12].

Both Cushing's syndrome due to PNHC and Cushing's disease are characterized by elevated levels of cortisol in the blood. Cushing's disease specifically refers to a tumor of pituitary gland releasing large amounts of ACTH which usually is found in the blood at basal level just over the normal upper limit (≤ 60 pg/ml). Conversely, in PNHC basal ACTH levels are usually very high (200–10,000 pg/ml) and, characteristically, do not re-

spond to negative feedback on pituitary gland from the high levels of cortisol or to the suppression test with high dose of dexamethasone; similarly, the stimulatory test with metirapone is ineffective.

When Cushing's syndrome is suspected, a dexamethasone suppression test and a 24-hour urinary measurement for cortisol offer equal detection rates. A novel approach is sampling cortisol in saliva over 24 h; late-night levels of salivary cortisol are high in Cushingoid patients. Other pituitary hormone levels may need to be ascertained. When any of these tests are positive, CT scanning of the adrenal gland and MRI of the pituitary gland are performed to detect any adrenal or pituitary adenomas. Adrenal scintigraphy with iodocholesterol is occasionally necessary.

The radical treatment of the underlying tumor or a neoplastic debulking can determine the resolution of the syndrome or symptom relief, respectively. Palliative treatment with steroidogenesis inhibitors (metirapone, aminoglutetimide, mitotane-DDD, ketoconazole, etc.), glucocorticoid antagonists (mifepristone) and somatostatin analogs can be also employed for symptom relief. Effectiveness of ketoconazole has been reported with ectopic ACTH production due to SCC of the prostate [11]. Bilateral adrenalectomy with timely substitutive corticoid therapy should be considered in refractory PNHC or preliminarily to anticancer treatments [13].

PNS of Inappropriate ADH Production

The syndrome of inappropriate production of ADH (SIADH) is defined by hyponatremia and hypo-osmolality, caused by aberrant continued secretion of ADH despite normal or increased plasma volume. Paraneoplastic SIADH is usually caused by tumors with neuroendocrine differentiation. The syndrome has been reported in association with SCC of genitourinary organs and in some cases of poorly or undifferentiated PCa [14–18].

Arginine vasopressin, the naturally occurring ADH in humans, is released into the circulation by neurons of posterior pituitary and its primary role is to promote the reabsorption of water along the course of the renal distal tubules and collecting ducts (hydro-osmotic effect). A second action of ADH is to cause arteriolar vasoconstriction rising arterial blood pressure (pressor effect).

In SIADH, the release of ADH is not inhibited by a reduction in plasma osmolality when the individual ingests water, resulting in dilutional hypotonic hyponatremia and related clinical consequences: headache, nausea, vomiting, convulsion, confusion and coma. Edema is absent and blood pressure usually normal.

SIADH is still best identified by the classic criteria defined by Bartter and Schwartz in 1967: hyponatremia (serum sodium <135 mM) and hypo-osmolality (serum osmolality <280 mosm/kg); continued renal excretion of sodium; urine less than maximally dilute; absence of clinical evidence of volume depletion; normal skin turgor and blood pressure; correction of hyponatremia by fluid restriction; absence of other causes of hyponatremia such as hypovolemia, adrenal or pituitary insufficiency, hypothyroidism, cardiac failure, renal or hepatic disease, drugs impairing renal water excretion. The plasma ADH is typically elevated, but its determination is not crucial for the diagnosis of SIADH.

When surgical treatment of the underlying tumor is not possible, SIADH is usually treated with fluid restriction, administration of hypertonic sodium chloride solution (3%) and diuretics, taking care not to correct water imbalances too rapidly (risk of pontine myelinolysis). Urea is a good alternative in refractory SIADH. The prolonged use of demeclocycline, blocking ADH-dependent synthesis of cAMP in distal renal tubules, could lead to important hepatotoxicity. Antagonist of tubulorenal vasopressin receptors, such as conivaptan and tolvaptan, can raise the serum sodium in hospitalized patients. Corticosteroids are only indicated when adrenal or pituitary insufficiency cannot be ruled out.

Syndrome of Inappropriate Serotonin Production

The inappropriate secretion of serotonin (5-HT) by neuroendocrine tumors is usually associated with inappropriate secretion of other substances (e.g. kallikrein, bradykinin, histamine, prostaglandins, neuropeptides). Neuroendocrine tumors can affect genitourinary organs, particularly prostate. The syndrome is similar to the so-called 'carcinoid syndrome' caused by intestinal and bronchial carcinoid tumors. Carcinoids occur in less than 1% of cases in other sites including kidney, testes, bladder, urethra and prostate [19], although some authors have questioned the real existence of 'primary prostatic carcinoid tumors' that may represent adenocarcinomas with carcinoid-like areas. The syndrome of inappropriate 5-HT production has been described in some patients with neuroendocrine tumors of genitourinary organs, although the syndrome is absent in most of these patients [20, 21].

Clinical findings include: flushing of the skin (85%), diarrhea and abdominal pain (80%), right-sided heart disease (37%) and fibrosis of the tricuspid and pulmonary

valve, bronchoconstriction (17%), myopathy (7%), pigmentation (5%), arthropathy (5%).

Diagnosis is made primarily by measuring plasma levels of 5-HT and/or 5-HTP (5-hydroxytryptophan) and chromogranin A, supported by measuring the 24-hour urine levels of 5-HTP and/or 5-HIAA (5-hydroxyindoleacetic acid). Octreoscan and ^{11}C -5-HTP-PET may be of limited value for diagnosis of neuroendocrine tumors of urinary tract because of the high radioactivity of urine; however, they could be useful for diagnosis and monitoring of the development of recurrence or metastasis [22].

When radical oncological treatment is not achievable, symptomatic relief can be obtained by inhibitors of chemical mediators of the syndrome: octreotide (somatostatin analogue which neutralizes 5-HT), cyproheptadine (antihistamine and receptorial 5-HT antagonist) and parachlorophenylalanine (blocking 5-HT synthesis).

Syndromes of Inappropriate Growth Factors Production

Non-Islet-Cell Tumor Hypoglycemia

Non-islet-cell tumor hypoglycemia (NICTH) is a rare condition. Soft tissue sarcomas have been associated with NICTH in several reports. Seventy of 115 patients with sarcomas and NICTH had abdominal sarcomas, usually retroperitoneal such as adrenal or renal sarcomas [23]. NICTH is characterized by elevated IGF-II levels or abnormal high-molecular IGF-II-precursor proteins ('big IGF-2') and normal or decreased levels of IGF1, insulin and GH [24]. Increased levels of IGF2 (or big IGF-2)-mRNA could be detected in tumor tissues.

The hypoglycemia in NICTH could be related to the insulin-like receptorial activity of IGF-II, but a disturbed glucose metabolism or decreased hepatic gluconeogenesis seems to be also involved.

When radical surgery is not possible, symptoms may be controlled with glucose solution, glucagon, glyccorticoids, GH, somatostatin analogues, together with chemotherapy and/or radiotherapy.

Acanthosis Nigricans

Acanthosis nigricans (AN) is characterized by eruption of many, symmetric, velvety hyperkeratotic lesions with brownish hyperpigmentation. Flexures, skin folds, axillas, bend of the elbow, nipples, neck, navel and anogenital regions are predominantly involved.

The occurrence of AN in adult is almost in 100% associated with cancers. The syndrome is related to the inappropriate production of TGF- α , EGF and a MSH-like peptide by undifferentiated malignancies. Most often involved tumors are carcinomas (gastric especially), sarcomas and hematological proliferations. The occurrence of AN is rarely reported in urological cancers, such as RCC, BCa and PCa, and seems to be an indicator of a bad prognosis [25–27].

Paraneoplastic AN occurs in three abortive clinical subforms as *papillomatosis florida cutis verruciformis*, *tripe palmar syndrome* and *Leser-Trélat sign*. They coexist together or appear consecutively after each other. The malignant type of AN is characterized by its sudden onset, rapid progression, more expressed hyperkeratosis and hyperpigmentation with coexisting pruritus. Pathological lesions are mainly localized on the mucous membranes. The treatment is mainly based on the tumor-specific therapeutic options.

Paraneoplastic Leukocytosis

Paraneoplastic leukocytosis is common in cancers and has been described for RCC and urotheliomas [28–31]. It has been related to tumor production of granulocyte colony-stimulating factor (G-CSF) that promotes the development of mature neutrophils from hematopoietic progenitor cells.

The diagnostic criteria for G-CSF-producing malignancies include marked leukocytosis with predominant mature neutrophils, elevated serum G-CSF, positive immunohistochemical staining of tumor cells with anti-G-CSF antibody, leukocytosis and elevated serum G-CSF returning to normal after tumor removal.

Interestingly, receptors for G-CSF found on the cell surfaces of BCa cells may play an autocrine stimulatory role [32]. This may explain the bad prognosis of these tumors that may represent a distinct and highly aggressive subtype of BCa [31].

Fasciitis-Panniculitis Syndrome

The fasciitis-panniculitis syndrome (FPS) does not constitute a nosologic entity but is a stereotyped pattern of reaction involving the subcutaneous tissues, superficial fascia, and subjacent muscle [33]. Clinically, FPS is characterized by swelling and induration of the skin of the upper or lower extremities and sometimes of the trunk or neck. The indurated segments present large, circumferential sleeve-like or round to elongated patchy lesions. Chronic inflammation and fibrosis occur in the subcutaneous fat tissue and deep fascia [34].

The incidence of cancer in patients with FPS is rather small and a meticulous search for occult cancer does not seem cost-effective as long as additional indications are lacking. Occurrence of FPS has been sporadically reported in patients with PCa [34]. The pathogenesis of the cancer-associated FPS is unknown. The secretion of growth factors, such as PDGF, FGF, TGF- α and TGF- β , which stimulate collagen and extracellular matrix production, seems involved.

RCC-Related PNS

RCC is unique among the genitourinary malignancies in that close to one third of affected patients show signs and symptoms of a PNS. It is estimated that 10–40% of patients with this disease will develop a PNS.

Hypercalcemia and Cushing's syndrome have been discussed above. Some are present merely as associated serum findings, such as elevated human chorionic gonadotropin; others are quite rare, such as abnormalities in glucose metabolism and galactorrhea [35–37].

Aside from a handful of well-documented syndromes, many symptoms presumed to be related to RCC are assigned the designation 'paraneoplastic' following their remission after nephrectomy, even though this after-the-fact diagnosis may not represent actual causation by the tumor. Most PNS associated with localized RCC are definitively treated with nephrectomy only.

Constitutional Symptoms

Fever, anemia, weight loss, and fatigue can be the first symptoms of RCC in up to one third of cases. Fever is found in 20–30% of those with RCC and is the sole presenting complaint in approximately 2% of patients. These constitutional symptoms found in RCC are thought to be mediated by cytokines such as TNF- β , IL-6, IL-1, interferons and prostaglandins.

Anemia is observed in about 20% of RCC patients. Poor nutritional status and the presence of a chronic disease are two main reasons for the anemia that, however, has been also related to tumor production of iron-binding protein, such as ferritin and lactoferrin [38, 39].

Cachexia, defined as hypoalbuminemia, weight loss, anorexia or malaise, predicted worse survival after controlling for well-established indicators of prognosis in one study [40]. Once nonneoplastic causes of constitutional symptoms in patients with RCC have been ruled out, nephrectomy is the most effective treatment.

Hypertension and Inappropriate Renin Production

Hypertension is reported in 14–35% of RCC patients presenting with PNS [41]. Hypertension as the only presenting symptom in RCC is rare. Potential mechanisms of hypertension in RCC patients include increased renin secretion, presence of an arteriovenous fistula, and polycythemia [42]. Local renal parenchymal compression may lead to intrarenal ischemia and further increase renin excretion. Ureteral obstruction may cause renin secretion by a similar mechanism. Additionally, although rare, renin-secreting tumors may arise from the juxtaglomerular apparatus itself and, as expected, are associated with hyperaldosteronism and hypokalemia [43].

Hypertension is typically associated with low-grade, clear-cell tumors. Several studies have failed to demonstrate a clear relationship between the presence of hypertension and prognosis in RCC patients [40, 44, 45]. If diagnosed early, the hypertension is reversible with nephrectomy.

Polycythemia and Inappropriate Erythropoietin Production

Polycythemia has been noted in 1–8% of RCC cases. In these patients, elevated red blood cell concentrations are believed to be mediated by erythropoietin (EPO), a glycoprotein produced by peritubular renal interstitial cells that promote red blood cell production in the bone marrow. An inappropriate and often clinically silent EPO production occurs in up to 66% of RCC cases making this neoplasm the leading cause of ectopic EPO production [46]. The aberrant EPO production occurs in the tumor cells themselves, but perineoplastic cells may also contribute to total EPO levels secondary to local tumor compression and resultant tissue hypoxia [35, 47].

In those with organ-confined disease, EPO levels fall to normal following nephrectomy, whereas they remain elevated in those with metastatic disease. Similarly, EPO levels frequently rise with tumor recurrence when the primary lesion was associated with elevated EPO levels [48]. Therefore, a role for EPO as a marker of therapeutic response may exist in some cases.

Stauffer's Syndrome

Stauffer's syndrome is seen in 3–20% of RCC patients and is characterized by generalized hepatitis with lymphocytic infiltration, hepatocellular degeneration and elevations in liver enzymes as well as abnormal levels of hepatic synthetic products in the absence of hepatic metastasis and jaundice, even though an icteric variant has been reported [35, 49]. Elevations of transaminases, alka-

Table 3. NPNS reported in patients with urological malignancies

Syndrome	Clinical features	Associated urological cancers	Antibodies	Ref.
Peripheral neuropathy	The most common NPNS. It is usually a distal sensorimotor polyneuropathy that produces mild motor weakness, sensory loss, and absent distal reflexes. Subacute sensory neuropathy is a more specific but rare peripheral neuropathy. Dorsal root ganglia degeneration and progressive sensory loss with ataxia but little motor weakness develop.	SCC of prostate and bladder	Anti-Hu autoantibody can be found in the serum of some patients.	52, 53
Limbic encephalitis	Characterized by rapid development of irritability, depression, sleep disturbances, seizures, hallucinations, and short-term memory loss. Approximately 80% of patients with limbic encephalitis have MRI T ₂ hyperintensities involving medial temporal lobes. PET studies may show radionuclide uptake in the temporal lobes, even when the MRI is normal. Approximately 30% of patients respond to treatment of the tumor, usually a testicular cancer, and to immunotherapy.	Testicular cancer, SCC of prostate, RCC. Testicular cancer can be confined to the testis and may be found in a microscopic stage.	Anti-Ma2-associated encephalitis characteristically affects the limbic system, diencephalon, or upper brainstem and is associated with testicular cancer. Some patients (usually with SCC) have anti-Hu in the serum and CSF.	54–57
Paraneoplastic cerebellar degeneration	Paraneoplastic cerebellar degeneration is a heterogeneous group of disorders characterized by the subacute onset in cancer patients of a cerebellar syndrome: progressive bilateral leg and arm ataxia, dysarthria, vertigo, diplopia, nystagmus, ophthalmoplegia, dementia with or without brain stem signs, extensor plantar signs, with prominent dysarthria and arm involvement. The disease usually progresses over weeks to months, often causing profound disability. Cerebellar degeneration may precede the discovery of the cancer (usually SCC or breast and gynecologic tumors) by weeks to years. MRI or CT may show cerebellar atrophy.	BCa and PCa	Anti-Yo, a circulating autoantibody binding to cytoplasmatic protein antigens of Purkinje cells, and anti-Hu are found in the serum and/or CSF of some patients.	58, 59
Opsoclonus-myoclonus-ataxia syndrome	Opsoclonus (spontaneous chaotic eye movements) is usually associated with cerebellar ataxia and myoclonus of the trunk and extremities. Usually accompanying childhood neuroblastoma, in adults the most frequent causes are idiopathic (50%) and paraneoplastic (20%). This cerebellar syndrome has been reported in patients with lung, breast and gynecologic tumors.	RCC, adenocarcinoma and urothelioma of bladder	The autoantibody anti-Ri may be present in the serum and CSF directly resulting in the damage to the neurons causing the symptomatology.	60–63
Eaton-Lambert myasthenic syndrome	Eaton-Lambert myasthenic syndrome is an immune-mediated, myasthenia-like disorder of neuromuscular and autonomic transmission with weakness usually affecting the limbs and sparing ocular and bulbar muscles. It results from impaired release of acetylcholine from nerve terminals. The diagnosis is confirmed by serum test for autoantibodies and by finding an incremental response to repetitive nerve stimulation. The syndrome can precede, occur with, or develop after the diagnosis of cancer. It occurs most commonly in men with intrathoracic tumors such as lymphomas, thymomas or (70% of cases) pulmonary SCC.	PCa, prostatic SCC, BCa. The association of the syndrome with PCa can be a marker of neuroendocrine differentiation and hormonal independency.	An IgG autoantibody (anti-VGCC) leading to presynaptic voltage-gated calcium channel loss is involved (a serum test for anti-VGCC is commercially available).	64, 65
Stiff-person syndrome	A rare neurological disorder characterized by progressive muscle rigidity and superimposed spasms that predominate in the muscles of the trunk and proximal extremities. Less than 5% of cases have a paraneoplastic etiology. Tumors involved are breast cancer, SCC of lung and thymoma.	RCC	Most stiff-person syndrome patients have glutamic acid decarboxylase antibodies, and, especially in paraneoplastic forms, amphiphysin antibodies.	66
Myositis	Polymyositis and dermatomyositis are idiopathic inflammatory myopathy characterized by asthenia, pain, progressive hypertrophy of proximal muscles and dermatologic manifestations such as violet-colored rashes of the face and hands. There are some evidences of the autoimmune basis of paraneoplastic polymyositis and dermatomyositis such as the presence of a lymphoplasmal cellular infiltrate of the muscular interstices.	Most urological tumors		67–70

Fig. 1. Proposed pathogenesis of NPNS. A tumor not involving the nervous system expresses a neuronal protein that the immune system recognizes as nonself. Apoptotic tumor cells are phagocytized by dendritic cells that migrate to lymph nodes, where they activate antigen-specific CD4+, CD8+, and B cells. The B cells mature into plasma cells that produce antibodies against the tumor antigen. The antibodies or the cytotoxic CD8+ T cells (or both) slow the growth of the tumor, but they also react with portions of the nervous system outside the blood-brain barrier. In the illustration, antibodies are reacting with voltage-gated calcium channels at the neuromuscular junction, causing the Eaton-Lambert myasthenic syndrome. In some instances, plasma cells and cytotoxic T cells cross the blood-brain barrier and attack neurons expressing the antigen they share with the tumor. From Darnell and Posner [51], with permission.

line phosphatase, and prothrombin time exist in 66% of cases [50]. Clinically, patients may present with hepatosplenomegaly, fever, and weight loss.

The pathogenesis is still unclear. Some believe that the tumor itself secretes hepatotoxins or lysosomal enzymes that stimulate hepatic cathepsins or phosphatases, which leads to hepatocellular injury; others suggest that tumor-secreted hepatotoxins lead to hepatocyte injury with subsequent activation of the immune system. The aber-

rant tumor production of interleukin-6, known to stimulate hepatic protein production, may also play a direct role.

Neurological PNS

NPNS affect 6% of all patients with cancer. NPNS sporadically reported in patients with urological tumors are summarized in table 3. Currently, it is thought that most or all NPNS are immune-mediated (fig. 1). They may be caused by ectopic expression/release of antigens normally confined exclusively in the central nervous system. Some of these so-called onconeural antigens are also expressed in the normal testis, an organ that is, like the brain, an immunologically privileged site. Onconeural antigens are present in the tumor in all patients with antibody-positive NPNS and in many patients without such disorders. The neurological disorder usually appears before the cancer has been identified and develops rapidly. NPNS are usually severe, often disabling, and sometimes lethal.

Search for autoantibodies in cerebrospinal fluid (CSF) is very important to confirm the diagnosis and may suggest the site of the underlying cancer. The use of sensitive imaging techniques such as CT and PET combined studies are often required.

Radical treatment of the underlying tumor must be attempted. Immunosuppression by intravenous immunoglobulins, steroids, immunosuppressive drugs or by plasmapheresis should be reserved for patients with clearly identifiable antibodies in their serum [51].

Conclusions

All genitourinary tumors may cause a PNS, even though RCC is the most frequent urological malignancy involved. Although some PNS, such as polycythemia and hypertension, are more typical of RCC, others, such as hypercalcemia and Cushing's syndrome, are common to other genitourinary cancers. PCa is the second urological tumor associated with PNS which conversely are uncommon in BCa and rare in testicular cancer. Paraneoplastic hypercalcemia represents the most common PNS.

The neuroendocrine differentiation of tumors, such as PCa, SCC and carcinoids, is involved in most EPNS. Other syndromes, such as HHM, are associated primarily with genitourinary squamous phenotype.

When evaluating an individual with new onset neurological symptoms suggestive of PNS, clinicians should consider the presence of an underlying malignancy, including genitourinary carcinomas.

Any possible imaging study may be useful to detect the primary tumor in patients with PNS, and important advances have been made in radionuclide scan methods. The most effective treatment strategy is always represented by the radical therapy of the underlying cancer, even if specific therapeutic options are sometimes available.

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