Paraneoplastic Syndromes in Urologic Malignancy: The Many Faces of Renal Cell Carcinoma

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Renal cell carcinoma is unique among the genitourinary malignancies in that close to one third of affected patients show signs and symptoms of a paraneoplastic syndrome. The paraneoplastic syndromes associated with renal cell carcinoma range from those manifesting in constitutional symptoms (ie, fever, cachexia, and weight loss) to those that result in specific metabolic and biochemical abnormalities (ie, hypercalcemia, nonmetastatic hepatic dysfunction, amyloidosis, etc). The presence of a paraneoplastic syndrome in a patient with renal cell carcinoma is neither a marker of metastatic disease nor necessarily indicative of a poor prognosis. The importance of understanding the pathophysiology and biology behind the many paraneoplastic syndromes associated with renal cell carcinoma lies in the fact that the presence of these protean symptoms may be the initial presentation of either primary or recurrent disease. In this review, we will describe the proposed mechanisms of action of the many paraneoplastic syndromes associated with renal cell carcinoma as well as outline the clinical evaluation and treatment options currently available for these noteworthy disorders. [Rev Urol. 2002;4(4):163–170]

Key words: Renal cell carcinoma • Paraneoplastic syndrome • Kidney cancer

Today the classic triad of palpable mass, hematuria, and flank pain occurs in less than 15% of patients with renal cell carcinoma (RCC). It is estimated, however, that 10%–40% of patients with this disease will develop a paraneoplastic syndrome. Not uncommonly, either the initial manifestation of malignancy or the harbinger of cancer recurrence may be the presence of a paraneoplastic syndrome. The ability of RCC to induce a clinically evident metabolic abnormality

Table 1
Paraneoplastic Syndromes in Renal Cell Carcinoma

Endocrine	Nonendocrine
Hypercalcemia	Amyloidosis
Hypertension	Anemia
Polycythemia	Neuromyopathies
Nonmetastatic hepatic dysfunction	Vasculopathy
Galactorrhea	Nephropathy
Cushing's syndrome	Coagulopathy
Alterations in glucose metabolism	Prostaglandin elevation

has been known for over 50 years. As our awareness and understanding of this disease has increased, so too have the number of extrarenal manifestations attributable to this tumor. The term paraneoplastic syndrome refers to a constellation of systemic signs and symptoms that are second-

These syndromes exclude the sequelae of either direct tumor extension or metastasis.

ary to the presence of a malignancy. By definition these syndromes exclude the sequelae of either direct tumor extension or metastasis. These tumor-related syndromes may be the result of one of several factors: tumor production of humoral substances, or benign tissue production of humoral factors in response to renal malignancy or via the modulation of the immune system.

The initial evaluation of any patient begins with a thorough history and physical examination. When confronted with an abnormal physical sign, symptom, or laboratory value in the appropriate setting, as urologists we should keep in mind the many protean systemic manifestations of RCC. Indeed, historically this cancer has been called one of the "great

masqueraders" of medicine, because almost all organ systems have been affected by this disease. In the discussion below, we will describe the proposed mechanisms of action, signs/symptoms, differential diagnosis, laboratory evaluation, and treatment of the common and a few of the not-

so-common paraneoplastic syndromes associated with RCC. One approach to classifying these syndromes is illustrated in Table 1.

Hypercalcemia
Hypercalcemia may be seen in as many as 20% of patients with cancer. Among patients with RCC, it is

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the most common of the paraneoplastic syndromes, affecting between 13%–20% of patients.[1-3] Of those with hypercalcemia and RCC, approximately 75% have high-stage lesions.[4] Neither the presence nor

degree of hypercalcemia, however, has been shown to have a significant correlation with tumor grade or survival.[5] First described by Albright in 1941, hypercalcemia in RCC can be separated into two categories: metastatic and nonmetastatic.

Although hypercalcemia secondary to bony metastatic disease is not a true paraneoplastic syndrome, it deserves discussion because of its prevalence in patients with RCC. Approximately 50% of all patients with hypercalcemia and RCC have bone metastases.[6] Hypercalcemia due to bony metastatic RCC lesions is termed metastatic hypercalcemia. Osseous metastatic RCC lesions appear to elaborate substances that activate osteoclasts, causing the release of calcium from bone. The local secretion of prostaglandins by metastatic RCC lesions has also been implicated in the elevated serum calcium levels seen in these patients.[7] Clinically, this form of hypercalcemia is predominantly associated with complaints of bone pain, a symptom not usually noted in nonmetastatic hypercalcemia. Local radiation therapy of affected bony lesions is often very effective in alleviating pain. Medical treatment in the form of intravenous hydration, loop diuretics, and bisphosphonates may also be beneficial in managing the systemic disturbances associated with hypercalcemia seen in these circumstances.

Nonmetastatic hypercalcemia is

defined as the elevation of serum calcium levels in the presence of a tumor that has not spread to the bone. One proposed mechanism for this phenomenon involves the elaboration of hormonal peptides by renal

tumor cells. In 1964, Goldberg and colleagues examined autopsy specimens of patients with RCC who had hypercalcemia. They found that RCC tumor extracts reacted positively to radioimmunoassays for parathyroid hormone (PTH).[8] Subsequent research revealed that the substance produced by these tumor cells was a novel pro-

Hypercalcemia secondary to bony metastatic disease is not a true paraneoplastic syndrome.

tein, parathyroid hormone-related peptide (PTHrP). Experiments have since shown that RCC specimens produce both PTH and PTHrP. Interestingly, PTHrP is not considered to be a peptide that is unique to tumor cells. Its overproduction in malignant states is thought to be the result of altered gene expression.[9]

The mechanism by which PTHrP causes hypercalcemia involves many of the normal hormonal pathways of calcium homeostasis. PTHrP binds to the PTH receptor in both bone and renal tissue. This binding leads to increased bone resorption and decreased renal clearance of calcium as well as increased phosphorus excretion. Additionally, low levels of 1,25-(OH)2-D3 are seen due to renal inhibition of 1,25-hydroxylase.[10] Thus laboratory studies in affected patients reveal hypercalcemia, decreased levels of PTH and 1,25-vitamin D, as well as renal phosphate wasting.[5] This syndrome is similar to that of primary hyperparathyroidism except that those with RCC have decreased renal and intestinal calcium absorption in addition to decreased 1,25-vitamin D synthesis.[11] Additional factors such as transforming growth factor (TGF) α and β, osteoclast activating factor (OAF), interleukin 1 (IL-1), and tumor necrosis factor (TNF) are also believed to exacerbate the non-

metastatic hypercalcemia seen in RCC patients either by distinct mechanisms or by augmenting the actions of PTHrP.[1,7]

Clinically, hypercalcemia presents with a wide range of signs and symptoms affecting numerous organ systems. Patients may complain of lethargy, nausea, fatigue, confusion, weakness, and constipation. Physical examination may reveal decreased deep tendon reflexes and impaired level of consciousness. Signs of dehydration may also be present secondary to loss of renal concentrating ability and subsequent polyuria. Electrocardiogram (ECG) findings include increased PR and QT intervals with eventual bradyarrhythmias and asystole. As opposed to most other paraneoplastic syndromes, metastatic hypercalcemia is very responsive to medical therapy. Volume repletion can be accomplished with normal saline and total serum calcium can be reduced with loop diuretic (ie, furosemide) administration. Moreover, bisphosphonates are effective for long-term management of hypercalcemia. Some studies have also been able to lower the serum cal-

Local radiation therapy of affected bony lesions is often very effective in alleviating pain.

cium concentration with the administration of nonsteroidal anti-inflammatory drugs, such as indomethacin, when serum prostaglandin levels are elevated.[12] Despite these palliative measures, nephrectomy is the most effective way to treat the nonmetastatic hypercalcemia seen with RCC.[13]

Hypertension

Another common paraneoplastic syndrome found in those with RCC is hypertension. Whereas the incidence of hypertension among age-matched controls is close to 20%, almost 40% of those with RCC experience hypertension.[14] Hypertension is typically associated with low-grade tumors of clear-cell histology. Several studies have failed to demonstrate a clear relationship between the presence of hypertension in patients with RCC and prognosis.[15–17] Potential mechanisms of hypertension in these patients include increased renin secretion, ureteral or parenchymal compression, presence of an arteriovenous fistula, and polycythemia.[16,18]

Renin is the active form of the prohormone prorenin, which is secreted by the juxtaglomerular apparatus (JGA) of the nephron. Through its action via the renin-aldosterone-angiotensin system, renin overproduction may result in hypertension. Elevated serum renin levels have been found in 37% of patients with RCC and 87% of patients with Wilms' tumor.[19–21] Multiple sources of renin secretion in RCC exist. Neoplastic proximal tubular cells themselves may secrete renin, as evidenced by immunohistochemical studies on RCC tissues.[16] Local renal parenchymal compression, either from subcapsular hematoma or large

tumors, may lead to intrarenal ischemia and further increase renin excretion by the JGA.[22] Ureteral obstruction may cause renin secretion by a similar mechanism. Additionally, although rare, renin-secreting tumors may arise from the JGA itself and, as expected, are associated with

hyperaldosteronism and hypokalemia. Although they are benign in nature, resection of these tumors leads to resolution of hypertension in virtually all cases.[23]

Although 70% of RCC tumors are radiographically hypervascular, arteriovenous fistulae (AVF) are rare entities. Hypertension in these cases may be due to increased cardiac output or increased renin secretion secondary to ischemia distal to the fistula.[17] Interestingly, 70% of those with clinically significant AVF and RCC are female. In these cases, resolution of hypertension after nephrectomy is the rule.[24,25]

Although hypertension is not a prognostic indicator, the use of renin as a potential tumor marker has been investigated. Renin levels do not necessarily correlate with the degree of hypertension; however, they do decrease significantly after nephrectomy.[26] Therefore, treatment for hypertension caused by RCC is nephrectomy. This is highlighted by the fact that 85% of those with hypertension secondary to RCC are normotensive following tumor resection.[14,24]

Polycythemia
Polycythemia has been noted in 1%–8% of cases of RCC. In these patients, elevated serum red blood cell concentrations are believed to be mediated by erythropoietin (EPO), a glycoprotein that induces differentiation of erythrocyte colony-forming units in the bone marrow to promote red blood cell production.[27] Under normal physiological conditions, EPO is produced by peritubular renal interstitial cells in response to local tissue hypoxia. However, in RCC, EPO production occurs in the tumor cells themselves. In fact, ectopic EPO production is found in 66% of RCC cases, making this neoplasm the leading cause of ectopic EPO production.[21] In addition to neoplastic cellular produc-

tion of EPO, perineoplastic cells in RCC may also contribute to total EPO levels secondary to local tumor compression and resultant tissue hypoxia.[27,28]

Although two thirds of RCC patients have elevated EPO levels, only 8% experience erythrocytosis. There is evidence to suggest that tumor cells may produce an inactive form of EPO.[29] In fact, anemia is more commonly seen in patients with RCC than erythrocytosis. Poor

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The prevalence of elevated EPO levels in RCC has led to its study as a potential tumor marker.

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nutritional status and the presence of a chronic disease are two main reasons for the anemia seen in these patients. Lactoferrin, an iron-binding glycoprotein produced by RCC, has also been implicated in the anemia noted in RCC.[30]

The prevalence of elevated EPO levels in RCC has led to its study as a potential tumor marker. To date, elevated EPO levels have demonstrated no prognostic significance. 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.[31] Therefore a role for EPO as a marker of therapeutic response may exist in some cases.

Nonmetastatic Hepatic Dysfunction
In 1961, Stauffer noted hepatic abnormalities in a patient with RCC with no evidence of hepatic metastases. These abnormalities resolved with nephrectomy but returned with disease recurrence.[32] Seen in 3%–20% of RCC patients, the constellation of signs and symptoms associated with

these hepatic abnormalities is referred to as Stauffer's syndrome. The syndrome is characterized by elevations in liver enzymes as well as abnormal levels of hepatic synthetic products. Elevations of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and prothrombin time exist in 66% of cases. Additionally, elevated levels of gammaglobulin and bilirubin are seen in 54% and 27% of patients with

Stauffer's syndrome, respectively.[33,34]

The cause of Stauffer's syndrome is poorly understood. Some believe that the tumor itself secretes hepatotoxins or lysosomal enzymes that stimulate hepatic cathepsins or phosphatases, which leads to hepato-cellular injury.[35,36] A second theory suggests that tumor-secreted hepatotoxins lead to hepatocyte injury with subsequent activation of the immune system via the local recruitment of T cells and the production of antibodies against liver antigens.[35] Evidence also suggests that aberrant tumor production of interleukin-6 (IL-6), known to stimulate hepatic protein production, may directly play a role in Stauffer's syndrome because it is frequently produced by RCC cells.[37] Regardless of the exact mechanism of injury, liver biopsy in these patients reveals generalized hepatitis with lymphocytic infiltration and hepatocellular degeneration without biliary obstruction.[34]

Clinically, patients may present with hepatosplenomegaly, fever, and weight loss. Diagnosis, however, requires at least three of the previously described serum abnormalities to be present.[34] Treatment consists of nephrectomy, which leads to resolu-

tion of hepatitis in 66% of patients.[38] Although the presence of non-metastatic hepatitis is not a prognostic indicator, response of liver enzymes following nephrectomy has been shown to predict survival. The 1-year survival rate after nephrectomy for those whose liver enzymes normalize is 88% compared to 26% for those whose enzymes remain elevated.[39] Similarly, 90% of those patients whose liver enzymes do not return to baseline following nephrectomy eventually develop clinically detectable metastatic disease.[40]

Constitutional Symptoms

In up to one third of cases, symptoms such as fever, weight loss, and fatigue are the first symptoms of RCC.[19] Fever is found in 20%–30% of those with RCC and is the sole presenting complaint in approximately

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2% of patients.[41] Although nonspecific symptoms are common to many malignancies, research focusing on their etiologies may provide information on both the biology and the clinical behavior of associated tumors.

The constitutional symptoms found in RCC are thought to be mediated by cytokines. Patients with RCC are known to have elevated serum levels of TNF-α, a cytokine known to alter adipocyte metabolism and affect appetite control. Additionally, IL-6 has been studied as a possible pyrogen in RCC. In one study, 18 of 71 patients with RCC were found to have elevated levels of IL-6, and 78% of those with increased IL-6 levels had fever.[37] Finally, other cytokines such as IL-1 as well as certain interferons and prostaglandins have been evaluated as possible agents involved in

the constitutional symptoms associated with RCC.

Once nonneoplastic causes of constitutional symptoms in patients with RCC have been ruled out, nephrectomy is the most effective of treatment. Fevers in organ-confined cases frequently subside with nephrectomy but may return with disease recurrence.[42] Neither the presence at diagnosis nor regression following therapy of constitutional symptoms has been shown to affect survival significantly.

Miscellaneous Endocrine Abnormalities

Numerous other endocrine abnormalities have been associated with RCC. Some are present merely as associated serum findings, such as elevated human chorionic gonadotropin (HCG) or adrenocorticotropic hormone (ACTH). Others, however, manifest themselves as clinical syndromes such as galactorrhea, Cushing's syndrome, and hyper/hypoglycemia.

β-HCG, normally made by the syncytiotrophoblastic cells of the placenta, has been found in elevated levels in patients with RCC.[43] Elevated levels of this hormone in any adult male or nonpregnant female should suggest malignancy. High levels of β-HCG have been documented in up to 6% of those patients with RCC.[44] No relationship between survival or tumor grade or stage has been found in patients with RCC and elevated serum levels of β-HCG.[45,46] And, as in many other paraneoplastic syndromes, HCG levels fall following nephrectomy but may rise with disease recurrence.[43,45]

Abnormalities in glucose metabolism have also been described in

RCC. There are several case reports of hyperglycemia and hypoglycemia that have resolved after nephrectomy for RCC. This finding has led to research into possible factors that may be either secreted or stimulated by the tumor. Hormones such as insulin and glucagon have all been isolated from RCC tumor extracts.[47] Additionally, when glucose metabolic abnormalities exist, levels of intracellular insulin and glucagon measured by immunohistochemical staining in tumor sections are 100 and 25 times higher, respectively, than controls.[47] Levels of enteroglucagon, a member of the amine precursor/uptake and decarboxylation family of hormones, usually secreted by intestinal mucosa, have also been reported to be elevated in RCC.[48] In one particular case, a patient who initially presented with glucose intolerance and constipation was found to have clinically localized RCC. Both of these symptoms, as well as an elevated enteroglucagon level, resolved following nephrectomy.[49] Subsequent immunohistochemical analysis of histopathological sections from this tumor revealed high levels of enteroglucagon expression.

In 1961, a group from the Mayo Clinic first described a possible relationship between RCC and Cushing's syndrome.[50] Subsequently, RCC has been found to account for 2% of all neoplasms that are responsible for Cushing's syndrome. Although rare, Cushing's syndrome in RCC is believed to occur secondary to enzymatic conversion of pro-opiomelanocortin (POMC) to ACTH by the tumor. This ectopic ACTH then drives cortisol secretion by the adrenal glands. The diffuse adrenal hyperplasia seen in these cases appears to support this hypothesis.[50] The syndrome resolves with nephrectomy and partial adrenalectomy in almost all cases due to the reduction of pathological ACTH production, and recurrence of elevated

ACTH levels may be a sign of disease progression.[51] When performing nephrectomy on these patients, the surgeon should keep in mind the risk of postoperative Addisonian crisis.

Galactorrhea and elevated serum prolactin levels have been described in two cases of RCC.[52] However, because prolactin is not routinely measured in patients with RCC, and the breast requires priming by factors such as estrogen, progesterone, and corticosteroids in order to lactate, the actual

prolactin level resolved following nephrectomy. Immunological studies performed on the cells from this tumor identified a substance that cross-reacted with antiprolactin antibodies.[52]

Other Nonendocrine Paraneoplastic Syndromes

Other nonendocrine paraneoplastic syndromes have been described in RCC. Some of these are extremely rare and their association with RCC is not as well defined as many of

syndromes may shed some light on the clinical behavior of RCC.

Amyloidosis is a disease associated with the pathological production and deposition of fibril proteins between cells in a variety of tissues and organs in a wide variety of clinical settings. The condition is present in 3%–8% of those with RCC.[19] The amyloid protein found in those with RCC, termed AA protein, is identical to the form seen in the chronic systemic disease of amyloidosis. Of note is that AA protein is thought to be a derivative of the acute phase reactant SAA, a protein that may be elevated in cases of RCC regardless of amyloid status.[53] The mechanism of amyloid production in RCC is not well understood but may involve prolonged stimulation of the immune system by growth of the malignancy or tumor necrosis.[54] Symptoms of amyloidosis depend on the magnitude of the deposits and the particular organs affected. Initial complaints include weakness, weight loss, and syncope. Eventually, clinical findings are

> *Regardless of their prevalence, the study of uncommon nonendocrine related paraneoplastic syndromes may shed some light on the clinical behavior of RCC.*

incidence of hyperprolactinemia may be higher than presently suspected. An elevated serum prolactin level in any male or nonpregnant female should raise suspicions of a malignancy. In one documented case of a patient with RCC and galactorrhea, both the galactorrhea and the elevated serum

the previously described syndromes. Nonetheless, diseases such as amyloidosis have been found with a recognized incidence in conjunction with RCC and have been studied in some detail. Regardless of their prevalence, the study of uncommon nonendocrine related paraneoplastic

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Main Points

- The classic triad of palpable mass, hematuria, and flank pain occurs in less than 15% of patients with renal cell carcinoma (RCC), but 10%–40% of patients with this disease may develop a paraneoplastic syndrome.

- Hypercalcemia is the most common of the paraneoplastic syndromes in patients with RCC and of those with hypercalcemia and RCC, approximately 75% have high-stage lesions.

- Approximately 50% of all patients with hypercalcemia and RCC have bone metastases, hence this form of hypercalcemia is termed metastatic hypercalcemia.

- Local radiation therapy of affected bony lesions is often very effective in alleviating pain; medical treatment in the form of intravenous hydration, loop diuretics, and bisphosphonates may also be beneficial.

- Nonmetastatic hypercalcemia is defined as the elevation of serum calcium levels in the presence of a tumor that has not spread to the bone.

- Hypertension is experienced by almost 40% of those with RCC and is typically associated with low-grade tumors of clear-cell histology.

- In up to one third of cases, symptoms such as fever, weight loss, and fatigue are the first symptoms of RCC; fever is found in 20%–30% of those with RCC and is the sole presenting complaint in approximately 2% of patients.

- Other conditions associated with RCC include polycythemia, nonmetastatic hepatic dysfunction, galactorrhea, Cushing's syndrome, hyper/hypoglycemia, amyloidosis, and some neuromyopathies.

- Most paraneoplastic syndromes associated with localized RCC are definitively treated with nephrectomy only; the recurrence of a previous paraneoplastic syndrome should alert the physician to possible disease progression.

related to the specific organ systems affected, such as the cardiac, renal, and gastrointestinal systems.

Neuromyopathies have been described in cases of nonmetastatic RCC. Degrees of severity vary from nonspecific myalgias to bilateral phrenic nerve paralysis.[55] A case of amyotrophic lateral sclerosis in a patient with RCC that resolved after nephrectomy has also been reported.[56] There is evidence to suggest that some RCCs may secrete a substance that may mediate such neuromyopathies.[57] The neuropathies associated with RCC may be either sensory or motor. Unfortunately, the low frequency with which these syndromes occur along with RCC precludes prognostic value and a meaningful study of their mechanisms.

Numerous other syndromes such as light chain nephropathy and various vasculitides and coagulopathies have been described in patients with RCC. Similarly, abnormalities involving prostaglandins, fibroblast growth factors, and α-fetoprotein have also been reported. Although these phenomena are not commonly seen in patients with RCC, their associations may provide some insight into the pathogenesis of kidney cancer.

Conclusion

Paraneoplastic syndromes represent aberrant cellular activity in the face of malignancy. Neoplastic cells appear to undergo a transformation that alters gene expression. In addition to neoplasia, these gene regulation alterations may also result in the production of either eutopic or heterotopic factors. The elaboration of these substances and their sequelae constitute a paraneoplastic syndrome. Under normal physiologic conditions the kidney carries out several endocrine (ie, production of erythropoietin and renin) as well as metabolic (ie, regulation of calcium metabolism) functions. In

RCC, these processes may become unregulated, resulting in specific systemic derangements. Furthermore, the production of factors not usually produced by the kidney may also occur. As discussed above, most paraneoplastic syndromes associated with localized RCC are definitively treated with nephrectomy only. Aside from a handful of well-documented syndromes, many symptoms presumed to be related to RCC are assigned the designation "paraneoplastic" following the remission of symptoms after nephrectomy. This after-the-fact diagnosis, although clinically evident, may not represent actual causation by the tumor.

Regardless, the many protean manifestations of RCC should be kept in mind when initially evaluating the appropriate patient. In addition, when following a patient after a nephrectomy for RCC, the recurrence of a previous paraneoplastic syndrome should alert the physician to possible disease progression. The continued investigation of the many paraneoplastic syndromes associated with RCC may someday result in improved diagnostic and therapeutic modalities for this unique urologic malignancy. ■

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