

Cancer and the Kidney

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Cancer of the kidney is associated with a bewildering array of extrarenal symptoms, and conversely, tumors far removed from the kidney produce intriguing renal functional abnormalities.

A variety of extrarenal complications are seen with hypernephromas, most of which rarely accompany Wilms tumors which grow rapidly and generally occur before the age of 7. Wilms tumors are quite susceptible to radiation therapy and surgery, and are to be strongly suspected when hypertension and an abdominal mass are found in a small child. Unless treated, they rapidly cause death and usually leave little opportunity for the patient to develop the striking extrarenal manifestations seen with hypernephroma.

Among the fascinating complications of hypernephromas (Table 1) is first, the extremely slow growth rate of a sizable minority of them. I have seen patients known to have hematuria for up to three years prior to the time that the tumor was found and, on reviewing the intravenous pyelogram done at the onset of hematuria, seen evidence that a renal mass had been present all along. Those tumors which do grow slowly may result in generalized amyloidosis both in the kidney and elsewhere. Another peculiarity of the hypernephroma, which is almost unique to this tumor, is the disappearance of metastases once the primary tumor has been removed. In only a few instances has there been histologic evidence that the "metastatic" lesions were indeed derived from a renal cell carcinoma. Nevertheless, the phenomenon of spontaneous regression of metastases seems well es-

tablished and offers at least a gleam of hope for those in whom pulmonary metastases are found.

Perhaps equally remarkable is the finding of distant metastases many years after a renal cell carcinoma is removed surgically. The longest recorded survival between a diagnosis of renal carcinoma and the eventual death of a patient whose neoplasm was considered inoperable and left in place is 37 years.¹ Many patients have been reported to develop metastases 5, 10, and even 25 years after the resection of a hypernephroma. I have seen a patient who developed "solitary" metastases sequentially over a 19-year period before he succumbed. Unfortunately, while such cases stand out, metastases appear earlier in most patients and lead to death within two years in one third of patients.

Renal cell carcinoma also tends to extend via the renal vein lumen into the inferior vena cava. Such a circumstance is reported to occur in almost 10% of patients with hypernephromas,² and a substantial proportion of these tumors extends all the way up the vena cava into the right atrium.³ The extending tumor usually is restricted to the venous lumen without penetration of the vessel wall and, as a result, is generally removable in its entirety. Surprisingly, such vascular involvement alone does not appear greatly to alter the prognosis at 5 or 10 years,⁴ and extraction of the tumor mass is often both possible and desirable.

Fever, unexplained by infection, is a common concomitant of hypernephroma. Melicow and Uson⁵ have reported that 16% of 577 cases of renal carcinoma presented with fever, often with weakness, anorexia, and weight loss, without any urologic symptoms whatsoever. A much higher percentage combined these systemic manifestations with hematuria, an abdominal mass, or pain. Thus, it is not

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TABLE 1
Peculiarities of Hypernephromas

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1. Slow growth frequent
 2. Disappearance of metastases (rare)
 3. Cause of occult fever (FUO)
 4. Renal vein/vena cava spread
 5. Nonmetastatic hepatic dysfunction
 6. Benign nephrohepatomegaly
 7. Polycythemia, leukemoid reaction, eosinophilia
 8. Heart failure
 9. Spontaneous rupture of kidney
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uncommon for patients with hypernephroma to present with "fever of unknown origin" and a baffling clinical picture. The fever may be low-grade and constant or intermittent and hectic, temperatures reaching 39.5 C (103 F) and higher.

First described in 1961,⁶ a syndrome of non-metastatic hepatic dysfunction (NHDS) accompanies the systemic abnormalities mentioned above in some 10% of patients with hypernephromas,⁷ and presents with hepatomegaly which differs both functionally and histologically from the benign hepatomegaly frequently encountered with such tumors.⁸ Here, biochemical abnormalities include elevated serum alkaline phosphatase concentrations, hypoalbuminemia, and hyperglobulinemia. Liver biopsy may reveal non-specific inflammatory infiltrates, fatty deposition, degenerative and regenerative changes of liver cells, and areas of focal necrosis.⁸ The syndrome may mimic metastatic disease of the liver from which it must be distinguished in that it is potentially reversible after nephrectomy is performed; recognition of NHDS may suggest a diagnosis of previously unrecognized hypernephroma.

Reviews of polycythemia generally include hypernephroma in the list of causes, but in fact, polycythemia has been associated with this tumor in only 1% to 4% of most reported series.¹⁰ Actually, anemia is more the rule than the exception whether or not the patient has had significant hematuria.¹¹ Eosinophilia, thrombocytosis, leukocytosis, and even leukomoid reactions occur in significant association with hypernephromas.¹² Coupled with fever of unknown origin, or alone, such findings may present vexing diagnostic problems.

As in many other types of malignancy, thrombophlebitis accompanies renal cell carcinoma with some frequency. Varicocele, particularly when on the right, may be the first clue to the existence of a renal tumor.

Hypertension is recorded in more than 20% of the patients with hypernephroma and in some cases, at least, the hypertension has been cured by nephrectomy.⁵ In others, hypertension is not surgically correctable, and it is difficult to be sure that the tumor was causally related. The renal tumor most clearly associated with hypertension is the "juxtaglomerular cell" tumor. Neoplastically benign, this growth, originating in macula densa tissue, produces huge amounts of renin with resultant secondary hyperaldosteronism and the complications attendant upon that condition. It is mentioned here as a rare but fascinating renal tumor which produces signs and symptoms which may erroneously suggest the existence of renal arterial stenosis or venous obstruction secondary to the spread of renal adenocarcinoma or the hyperreninism sometimes associated with Wilms tumors.¹³

Uncommon but life-threatening vascular complications of hypernephromas include high-output congestive heart failure and spontaneous rupture of the kidney with hemorrhagic shock. Heart failure is attributable to highly vascular metastases with arteriovenous communications analogous to those observed in Paget disease.¹⁴ Spontaneous rupture produces massive retroperitoneal hemorrhage closely resembling a ruptured aortic aneurysm and is equally lethal.¹⁵

Renal Complications of Extrarenal Malignancies

Space does not permit a detailed discussion of the many abnormalities of renal function found in subjects with malignant diseases; however, I shall comment upon the fluid and electrolyte disorders which frequently occur (Table 2), and discuss the nephrotic syndrome associated with malignancy.

Hypercalcemia may result from bony metastases or the forced immobilization of acutely ill patients. Certain cases are the result of parathormone secreting tumors which function autonomously,¹⁶ and a growing number of reports have called attention to the existence of prostaglandin-secreting tumors producing hypercalcemia which may be reversed with indomethacin.¹⁷ The hypercalcemia caused by both hormone-secreting tumors is reversible with complete removal of the tumor. Persistence of hypercalcemia after the primary tumor is excised may reflect the other causes of hypercalcemia (see Table 2), or be the result of metastases which, like the parent tumor, also synthesize prostaglandins or parathormone.

Hypercalcemia, if severe, may have devastating

TABLE 2
Electrolyte Abnormalities with Nonrenal Malignancies

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1. **HYPERCALCEMIA**—producing severe volume depletion and functional renal failure, nephrolithiasis or nephrocalcinosis:
 - a. Metastases
 - b. Corticosteroid withdrawal/adrenal insufficiency
 - c. Prostaglandin-secreting tumors
 - d. Forced immobilization
 - e. Parathormone-secreting tumors

 2. **VOLUME DEPLETION AND HYPONATREMIA***—producing functional renal failure:
 - a. Hypoadrenalism of tumor replacement, amyloidosis, surgical ablation of the adrenals, disseminated intravascular coagulation (DIC).
 - b. Excessive diuretic therapy for peritoneal metastases or mechanical edema.
 - c. Rapidly developing ascites and edema
 - d. Extrarenal electrolyte losses: secretory diarrheas, villous adenomas, drug Rx hyperemesis, intestinal obstruction, malabsorption and carcinoid.

* To be distinguished from the syndrome of inappropriate ADH secretion (CNS tumor/metastases, vasopressin-secreting tumors, vincristine/cyclophosphamide therapy, and tricyclic anticonvulsants) where renal function does not specifically become impaired.

 3. **VOLUME DEPLETION AND HYPERNATREMIA**—with functional renal failure:
 - a. Diabetes insipidus of pituitary replacement, brain metastases, urinary outflow obstruction.
 - b. Impaired thirst mechanism—organic or functional results of cachectic illness.
 - c. Kaliopenic and hypercalcemic nephropathy
 - d. Nasogastric feeding—osmotic diuresis

 4. **KALIOPENIC NEPHROPATHY**—with impaired concentrating capacity and susceptibility to pyelonephritis:
 - a. Pernicious gastrointestinal electrolyte loss (see section 2)
 - b. "ACTH"-producing tumors
 - c. Juxtaglomerular cell tumors
 - d. Improper diuretic therapy
 - e. Lysozymuric and nonlysozymuric leukemias
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effects upon the kidney, producing severe volume depletion and functional renal failure, nephrolithiasis with infection and urinary outflow obstruction, or severe tubulointerstitial disease due to nephrocalcinosis.

Volume depletion and hyponatremia are frequent complications which plague the patient with malignant disease. Generically, the concurrence of volume depletion and hyponatremia reflects a state in which both sodium and water are lost from the body in large amounts but the net sodium loss exceeds the water deficit. Causes include adrenal insufficiency owing to tumor replacement, adrenal amyloidosis, surgical ablation of the adrenals as a therapeutic adjuvant, and disseminated intravascular coagulation. Ill-advised sodium restriction with vigorous diuretic therapy in an attempt to minimize mechanical edema or ascites due to peritoneal metastases is a reasonably common cause of hyponatremic volume depletion. The rapid development of ascites and edema in sodium-restricted patients is another cause. Massive electrolyte losses may occur through the in-

testinal tract as a result of the hyperemesis associated with cancer chemotherapy, the secretory diarrheas [amine precursor uptake and decarboxylation (APUD) syndromes], mucus-secreting intestinal tumors, intestinal obstruction, or malabsorption. Massive fluid losses may be seen in the carcinoid syndrome. The severe volume depletion attendant upon these complications may produce major abnormalities in renal function unless corrected.

Hyponatremia may also be seen in the presence of extracellular fluid volume expansion—the so-called syndrome of inappropriate antidiuretic hormone (ADH) secretion. Causes include vasopressin-secreting tumors (especially of lung), primary or metastatic intracranial malignancies, vincristine or cyclophosphamide therapy to retard tumor growth, and the tricyclic anticonvulsants.¹⁸

Volume depletion may coexist with hypernatremia for a variety of reasons. Diabetes insipidus may result from tumor invasion of the pituitary gland, intracranial metastases, or urinary outflow obstruction. Nasogastric feeding of concentrated solu-

tions lacking in free water is a common cause of an obligatory solute diuresis. Impaired thirst due to either organic brain disease or as a functional result of a cachectic illness may contribute greatly to the development of hypernatremic volume depletion, a situation which is further aggravated if kaliopenic or hypercalcemic nephropathy is present.

Kaliopenic (hypokalemic) nephropathy is manifested by impaired concentrating capacity and an increased susceptibility to pyelonephritis. It may result from pernicious gastrointestinal electrolyte losses, hyperadrenal corticoidism secondary to an adrenocorticotrophic hormone (ACTH)-producing tumor, juxtaglomerular cell tumors, or improper diuretic management. Major degrees of hypokalemia may be seen in patients with leukemia, especially those leukemias associated with lysozymuria.¹⁹ Impaired concentrating capacity may well lead to serious volume depletion and secondary renal dysfunction.

Nonelectrolyte-related abnormalities of the urinary tract are listed in Table 3, but cannot be covered in detail in this brief review.

Nephrotic Syndrome Associated with Malignancy

An increasing number of reports amply document the association of the nephrotic syndrome with

malignant tumors.²⁰ Some cases are the result of amyloidosis, others to renal venous outflow obstruction, and still others to probable immune mechanisms. Myeloma and lymphoproliferative disorders are among the most common tumor-related causes of amyloidosis, yet solid tumors also may cause amyloid deposition if their course is not an accelerated one.²² Invasion of the renal veins and vena cava by hypernephromas or other tumors, and compression of venous structures by retroperitoneal nodes, tumor mass, or retroperitoneal fibrosis may produce mechanical edema and marked proteinuria but are uncommon causes of the nephrotic syndrome.

Tumor-related nephrotic syndrome occurs with some frequency in the absence of either amyloidosis or venous obstruction, Hodgkin disease leading the list of causes.²¹ Lymphosarcoma, chronic lymphocytic leukemia, and Burkitt lymphoma also have been associated with frank nephrosis.²¹ Of the solid tumors, bronchogenic carcinoma has been the most often found. Malignancies of the stomach, colon, breast, skin, ovary, oropharynx, and kidneys have all been incriminated.

The majority of lymphoma-related cases have shown minimal glomerular changes on biopsy or postmortem study. Most other types of tumors have produced membranous, proliferative or mixed membranous and proliferative lesions. Reversal of the nephrotic syndrome after excision or chemotherapy of the primary tumor has been observed by many authors, the return of proteinuria signaling regrowth of the malignancy.²¹

In this overview, I have tried to touch on the highly complex interaction between carcinomatosis and the kidney. The manifestations of this relationship are so diverse and numerous that it is well to remember the adage, "Many a medical reputation has been lost in the retroperitoneum." It is hoped that continued awareness of the protean manifestations of tumors relating to the kidney will help to preserve the reputations of all clinicians.

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TABLE 3
Nonelectrolyte Renal Complications of Malignancies

1. Fanconi syndrome
2. Renal tubular acidosis
3. Hydronephrosis—obstructive renal failure
4. Renal amyloidosis
5. Urate nephropathy
6. Radiation nephritis
7. "Citrovorum rescue," antimetabolite nephropathy
8. Myeloma kidney
9. Renal hemorrhage, outflow obstruction
10. Cortical necrosis post-disseminated intravascular coagulation (DIC)
11. Tumor-related lupus erythematosus (especially with lymphoma)
12. Renal vein/arterial or vena caval occlusion
13. Vasomotor nephropathy—hemorrhage, sepsis, shock, and so forth
14. Nephrolithiasis/nephrocalcinosis
15. Obstruction of bladder outflow, ureters, or urethra by tumor invasion
16. Renal invasion by metastases
17. Benign nephromegaly, etiology unknown
18. Retroperitoneal fibrosis/tumor invasion, producing ureteral obstruction
19. Nephrotic syndrome
20. Acute papillary necrosis, pyelonephritis

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