

The Presentation of Renal Carcinoma

By Robert A. Ball, M.D.

Renal cell carcinoma may present in a myriad of ways, masquerading behind diverse symptomatology which may make its diagnosis difficult even for the most wary of clinicians, thus the appellation, "the internist's tumor". Successful treatment of renal cell carcinoma requires tumor identification at an early stage, yet unfortunately, the classic signs of a renal cancer (gross hematuria, flank pain and renal mass) often represent advanced disease. However, not all signs and symptoms caused by renal cell carcinoma imply advanced disease nor do they have prognostic implications. Many are, in fact, reversible following treatment of the cancer. The following is a review of the clinical presentations of renal cell carcinoma in the adult with note of the improved survival following diagnosis of incidentally identified tumors.

Epidemiology and Etiology

Renal cell carcinoma, albeit, the third most common genito-urinary malignancy is relatively rare, making up only 2-3 percent of all adult malignancies with an incidence of approximately 8-10 per 100,000 men and 4-5 per 100,000 women. This includes 25,000 new cases and 9,000 deaths per year. The most common histo-pathologic pattern is the clear cell type adenocarcinoma which resembles adrenal cortical tissue, and hence, its acronym "hypernephroma". Other cell types include the granular cell, tubulo-papillary, and sarcomatoid variants. Renal cell tumors typically present in the fifth to seventh decades of life, rarely in patients less than 40, with median age of diagnosis of 64 years in whites and 58 years in African Americans.

The etiology of renal cell carcinoma (RCCA) is poorly understood. Electron microscopic studies are consistent with the tumor arising from proximal convoluted tubule cells. Although there is no one known etiologic agent, an association of increased incidence is noted for several risk factors. Von Hippel-Lindau syndrome patients have a 35-38 per cent incidence of developing RCCA during the course of their lifetimes. Patients with autosomal dominant polycystic kidney disease and acquired renal cystic disease following commencement of dialysis for end stage renal failure are also at increased risk. There are several genetic anomalies associated with

RCCA, the most prevalent being a loss of the short arm of chromosome 3, often associated with a 3p to chromosome 8 translocation. Occupational hazards appear to include exposure to cadmium, lead acetate, dimethylnitrosamines, dibromopropyl phosphate, petroleum distillates, and the radiographic agent, colloidal thorium dioxide. There is an increased risk to coke oven workers, newspaper pressmen and petrochemical plant workers. . Interestingly, there appears to be an increased risk in higher socioeconomic groups such as white collar workers and urban dwellers.

Other associated risk factors include tobacco use, obesity and estrogens. Tobacco use by either inhaled smoke or chew increases one's risk by a factor of 1.1-2.3 fold. This risk is directly related to the total length of exposure to the tobacco product. Obesity, particularly in females, is statistically significantly associated with RCCA. Early obesity which is maintained or exacerbated throughout life appears to increase risk. Finally, diethylstilbestrol exposure, which is utilized in high doses to induce RCCA in the experimental Syrian hamster model, is also believed to have potential effects as either an initiator or promoter of the disease in humans.

Clinical Presentation

Due to the location of the kidney deep in the retroperitoneum, enormous growth of a renal mass may occur prior to the development of signs or symptoms. In order for these tumors to cause symptoms they must either obstruct urine flow, bleed into the urinary collecting system, invade adjacent organs, or metastasize to distant sites. Thus, clinical symptoms often define extensive tumors. The classic triad of flank pain, hematuria and renal mass is noted in only 4-9 per cent of patients presenting with RCCA and parenthetically, of those, 50 per cent will be found to harbor disease. Conversely, up to 39 per cent of patients will have no symptoms referable to the GU tract. The incidence of symptoms accompanying the findings of RCCA include: flank pain in 41 per cent, hematuria in 38 per cent (gross hematuria 18-22 per cent), flank mass in 24 per cent, weight loss in 36 per cent, fever in 18 per cent, hypertension in 22 per cent, and acute varicocele in 2-11 per cent. Also, the potential of the abnormal renal adenocarcinoma cell of proximal tubule cell origin enables it to secrete a plethora of hormones, growth factors and polypeptides, resulting in systemic syndromes with a cadre of different signs.

Stauffer's syndrome, a non-metastatic hepatopathy resulting in serum liver function test anomalies occurs in 13-38 percent of RCCA patients without evidence of hepatic tumor involvement. Most patients with Stauffer's syndrome reveal elevation of alkaline phosphatase, prothrombin time, alpha globulin, and hypoalbuminemia levels. Also, associated are hyper-bilirubinemia, hypercholesterolemia and increased serum glutamyl transpeptidase. Half of the patients affected with Stauffer's syndrome present with a diffuse non-tender hepatomegaly. The diagnosis of Stauffer's syndrome is made by three biochemical anomalies with no evidence of hepatic metastasis by either imaging modality or direct exploration of the liver. The etiology of Stauffer's syndrome is cryptic, but believed to be secondary to tumor elaboration of hepatotoxin. The elevated LFT's have no prognostic significance preoperatively, returning to normal in approximately 70 per cent of patients following radical nephrectomy. Liver function tests that do not normalize post operatively, however, are associated with a 90 per cent incidence of occult metastatic disease with a 20 per cent 1 year survival, contrasted to an 88 per cent 1 year post operative survival in patients with normalized LFT'S.

A hypercalcemic syndrome is noted in approximately 13 per cent of RCCA patients at presentation. Although lytic bone metastasis of RCCA can cause hypercalciuria, a benign pseudohyperparathyroidism secondary to a parathyroid-like peptide secreted by the cancer may also be the etiology. As well, tumor associated transforming growth factor alpha as well as Prostaglandin E 1 can cause hypercalcemia. 75 per cent of patients with hypercalcemia at the time of diagnosis of RCCA have high stage disease.

Hypertension can be noted in up to 40 per cent of RCCA patients (compared to an approximately 20 per cent incidence in age match controls). Hyperreninemic mediated hypertension can be due to: a) direct tumor production and secretion of the renin precursor prorenin, b) secondary tumor mass affect causing renal artery stenosis and a "Goldblatt 2 kidney, 1 clip affect", or c) intrarenal capsular hemorrhage resulting in local renal ischemia and increased renin production. Other tumor associated causes of hypertension include arteriovenous fistula, ureteral obstruction secondary to tumor or blood clot, or brain metastases. Hypertension secondary to the affect of locally confined renal cell carcinoma virtually has no prognostic significance, however, return of hypertension after nephrectomy is often a sign of tumor recurrence.

Hematologic manifestations of RCCA include erythrocytosis found in 3-10 per cent of patients and is secondary to elevated levels of erythropoietin which are either abnormally produced by the tumor or by normal

functioning renal parenchyma secondary to local ischemic effects caused by tumor mass. Tumor induced production of lactoferrin, an iron binding glycoprotein, is believed to result in anemic states. As many as 25 per cent of RCCA patients have decreased serum iron.

Pyrexia, noted in 12-20 per cent of patients is the sole presenting symptom in 2 per cent of RCCA patients, and is associated with the granular cell variant. Tumor induced release of tumor necrosis factor (cachexin) and IL-1 (endogenous,,pyrogen) are the likely causes. Pyrexia has no prognostic influence.

Other less common associated signs and symptoms include: 1) galactorrhea secondary to tumor secretion of prolactin, 2) Cushing's syndrome, 3) carcinoid-like syndromes secondary to increased Prostaglandin production, 4) a hypercoaguable state due to decrease in cyclo-oxygenase pathway metabolates, 5) dysfibrinogenemia with prolongation of thrombin time and reptilase time, 6) carcinomatous neuropathy including peripheral sensory motor dysfunction, neuropsychiatric disorders or diaphragmatic paralysis, 7) amyloidosis, 8) endocrinopathies such as hyperinsulinemia, hyperglycogenemia and elevated levels of chorionic gonadotropin and alpha-fetoprotein, and finally 9) systemic vasculitities, possibly secondary to increased basic fibroblastic growth factor.

Although RCCA is associated with a multitude of symptomatic syndromes, it appears that the best chance for cure in these patients is to find tumors at a low stage when they are asymptomatic. Historical five year survival statistics for RCCA are: Stage I (confined within the renal capsule), 60-85 per cent (mean 79 per cent); Stage II (confined within Gerota's fascia), 51 per cent; Stage IIIA (renal vein or inferior vena caval involvement without venous wall invasion), 33-68 per cent; Stage IIIB (positive lymphadenopathy), 16 per cent, and Stage IV (distant metastases), 2 per cent. The presence or absence of metastases, excluding solitary pulmonary metastases, which harbor a 22-35 per cent 5 year survival after total resection, is the single most important factor in determining survival.

Multiple studies have shown that increased numbers of patients are being diagnosed with RCCA incidental to evaluation of non-urologic complaints and these patients appear to have improved survival statistics. In order to determine the disease specific survival and impact of early diagnosis of renal carcinoma, The author reviewed all available charts of patients with the diagnosis of RCCA treated at the Peter Bent Brigham and Brigham and Woman's Hospital between 1980 and 1985. 176 patients with long term follow up were evaluated during that time.

Pathologic staging revealed diagnosis at: Stage I, 79 patients (46 per cent); Stage II, 23 patients (14 per cent); Stage III, 33 patients (20 per cent); and Stage IV, 31 patients (18 per cent). Immediately evident from comparison to historical studies of RCCA incidence was a stage migration revealing nearly half of the patients in this study, 46 per cent, were initially identified in the most curable Stage I disease. This compares favorably with historical studies noting 28 per cent initial Stage I presentation. Of the Stage I patients, 47 (60 per cent) were found serendipitously during an evaluation of non-urological complaints. The median age diagnosis was 57 years with a male/female ratio of 1.5-1. Interestingly, no patient in Stages I or II had the classic triad of flank pain, hematuria or renal mass. Most impressive was the 99 per cent disease specific survival of all Stage I patients at a mean follow up of 7.6 years. This compares most favorably to historic 5 year survival statistics of approximately 79 per cent. Other studies confirm these results with up to 95 per cent 5 year survival for Stage I renal cell carcinomas in patients found to harbor asymptomatic, incidentally found tumors. In other studies comparing incidentally found Stage I renal cell carcinomas versus those found during evaluation of genitourinary symptoms, those with symptoms had a significantly decreased 5 year survival at only 61 per cent. Therefore, it appears that albeit renal cell carcinoma is associated with a number of symptomatic syndromes, the best chance for cure is early detection of the tumor while it is confined within the capsule of the kidney, and this often requires detection prior to the onset of symptomatology.

References:

1. Sole-Balcells, F. & Villavicencio, M. Advances in the diagnosis of renal cell carcinoma. *Current opinions in Urology*, 1:25,1991
2. Pritchett, J.R., Lieskovsky, G., Skinner, D.G.: Clinical manifestations and treatment of renal parenchymal tumors. In: *Diagnosis and Management of Genitourinary Cancer*, Ed. by: Skinner, D.G., Lieskovsky, G. Chapter 19. pp 339-361, 1988. W.B. Saunders Co., Phila., PA.
3. de Kernion, J.B. & Belldegrun, A.: Renal tumors. In: *Campbell's Urology*, Ed. by: Walsh, P.C. et. al. Chapt. 27, pp 1053-1092, 1992. W.B. Saunders Co., Phila., PA.
4. Sufrin, G., et. al.: Paraneoplastic and serologic syndromes of renal adenocarcinoma. *Semin. in Urol.*, 7; 158, 19 8 9
5. Ball, R.A.: Richie, J.P.; Disease specific survival for low stage renal cell carcinoma. Unpublished data.

6. Thompson, I.M. & Peek M.: Improvement in survival of patients with renal cell carcinoma - the role of the serendipitously detected tumor. J. Urol., 140: 487, 1988.
7. Tosala, A. , et. al. Incidence and properties of renal masses and asymptomatic renal cell carcinoma detected by abdominal ultrasound. J. Urol., 144: 1097, 1990.
8. Aso, Y. & Momma, Y. : A survey of incidental renal cell carcinoma in Japan. J. Urol., 147: 340,1992.