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Management of advanced renal cancer

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CASE PRESENTATION

A 58-year-old man was referred to the medical oncology department of the Beth Israel Deaconess Medical Center in Boston 2 years ago by his primary care physician because of newly documented renal and lung masses. He had presented to his primary care physician a few weeks earlier for evaluation of decreased libido. Examination revealed a right-sided varicocele. Workup for the varicocele included an abdominal computerized tomography (CT) scan, which revealed bilateral complex renal masses, an 8 cm mass in the mid-portion of the right kidney, and a 2.5 cm mass involving the upper pole of the left kidney. Chest CT scan showed multiple bilateral pulmonary nodules, the largest being 1 cm in diameter. His past medical history was significant for hypertension and allergic rhinitis. He had no significant history of cardiopulmonary disease. His medicines included lisinopril and nasal steroids. There was no family history of renal cancer. He had a 20 pack-year history of smoking, but he had not smoked for more than 10 years.

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Physical examination in the oncologist's office revealed a healthy appearing middle-aged man. His weight was 219.7 pounds. The blood pressure was 160/100 mm Hg. His Eastern Cooperative Oncology Group (ECOG) Performance Status was zero. Aside from a right-sided varicocele, the examination was otherwise unremarkable. Specifically, there was no palpable abdominal mass or organomegaly.

Magnetic resonance imaging (MRI) of the abdomen with reconstruction images confirmed the presence of bilateral renal masses and showed evidence of tumor thrombosis involving the right renal vein extending to the junction with the inferior vena cava. No retroperitoneal adenopathy was identified. A bone scan and head CT disclosed no evidence of metastases. The hemoglobin was 13.7 g/dL, and the calcium and lactate dehydrogenase (LDH) levels were normal. An electrocardiogram, pulmonary function test, and an exercise stress test were unremarkable.

The patient was referred to a urologist, who performed a right cytoreductive "debulking" nephrectomy. Pathology showed clear cell renal cell carcinoma (RCC) with alveolar, but no papillary or granular, features. Surgery was uncomplicated and the patient had a quick recovery. Upon recovery, he received high-dose interleukin-2 (IL-2) therapy according to the standard regimen: 600,000 IU/kg every 8 hours on days 1 to 5 and 15 to 19. IL-2 therapy was associated with several typical side effects, including transient hypotension, weight gain, renal insufficiency, bilirubinemia, and pruritus. Treatment produced complete regression of most of the pulmonary nodules; however, a residual 7 mm right pulmonary nodule and the left renal mass persisted. An additional cycle of high-dose IL-2 three months later failed to produce additional tumor regression.

The patient was observed for several months, during which time the lung and renal lesions persisted. Six months after initiating IL-2, he was referred for video-assisted thoracoscopic resection of the lung lesion. Residual renal cancer was detected in the pathology specimen. The left renal mass was treated with radiofrequency ablation. A followup CT scan 2 months later demonstrated disease progression with multiple new lung nodules. Various experimental options were considered, and he was

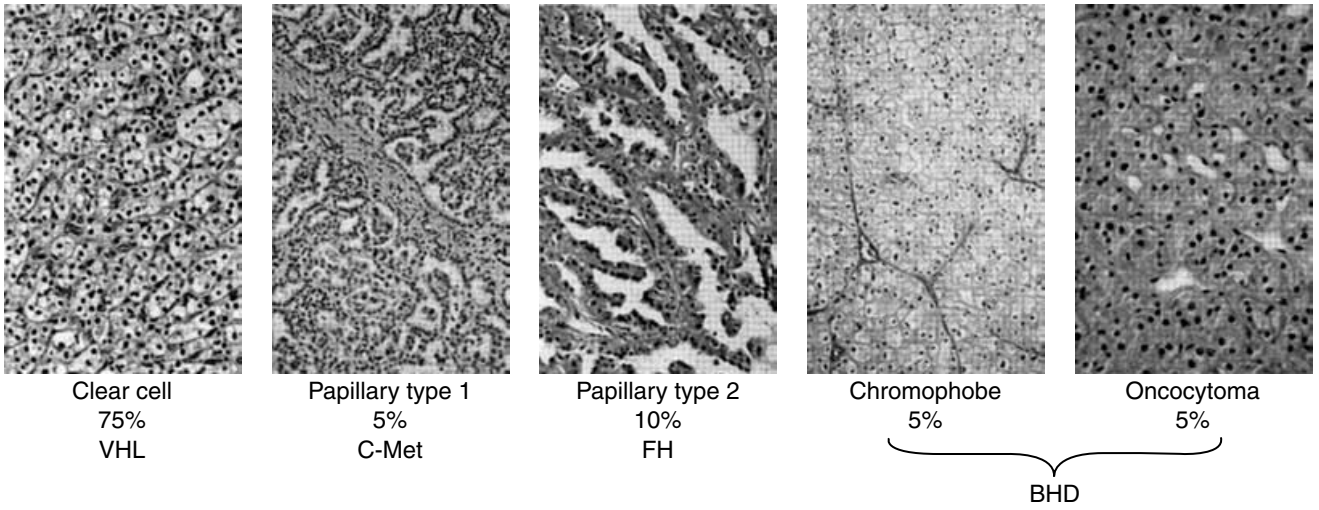

Fig. 1. Various histologic patterns, frequencies and characteristic genetic mutations seen in renal cancer. Abbreviations are: VHL, von Hippel-Lindau disease; FH, fumarate hydratase; BHD, Birt-Hogg-Dubé syndrome. (Adapted with permission from Linehan WM et al, *Clin Cancer Res* 10:62825–62895, 2004.)

eventually enrolled in a research protocol involving sorafenib (BAY 43-9006), an orally administered raf kinase inhibitor. Therapy was associated with fatigue, hand rash, and elevated blood pressure. After 12 weeks of treatment, restaging CT scans showed a 25% regression in tumor volume. His therapy was continued, but disease progression in bone was documented 6 months after initiation of treatment. The protocol therapy was halted.

DISCUSSION

DR. MICHAEL B. ATKINS (*Professor of Medicine, Harvard Medical School; Deputy Chief, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center; and Leader, Renal Cancer Program, Dana Farber/Harvard Cancer Center; Boston, Massachusetts, USA*): This patient depicts a fairly typical presentation and course for advanced RCC. His history highlights several issues related to the epidemiology, presentation, and treatment of renal cancer. Treatment issues raised by his illness include (1) the role of cytoreductive nephrectomy in patients presenting with stage IV disease, (2) the role of cytokine-based immunotherapy for stage IV renal cancer, (3) prognostic and predictive factors, (4) the role of salvage surgery in patients with partial response to cytokine-based therapy, (5) the emerging role of molecularly targeted and antiangiogenic therapy, and (6) the persistent need for improved therapy. All these issues will be discussed in the context of this case.

Malignant tumors of the kidney make up 3% of new cancer diagnoses and deaths each year in the United States. Approximately 32,000 cases and 12,000 deaths were anticipated in 2004 [1]. Renal cell cancer, which represents the vast majority of kidney tumors, occurs more often in men than in women. The mean age at diagnosis is around 60 years. The incidence rates for RCC have been rising each year in the United States since the 1970s, with recent increases being more rapid among blacks than whites. The worldwide incidence is highest in Scandinavia and other parts of northern Europe and in North America. The lowest rates are reported in India, China, Japan, and areas of Central and South America.

Most of the information on risk factors for RCC has come from case-control studies, with the largest studies comprising 1732 cases and 2309 controls [2–4]. Cigarette smoking is an established causal risk factor for RCC, with the relative risk among smokers from case-control and cohort studies ranging from 1.2 to 2.3 [2]. Approximately 20% to 30% of RCCs in men and 10% to 20% in women can be accounted for by cigarette smoking. Obesity, particularly in women, has been associated with RCC [3], as has hypertension. Some studies have suggested that the use of certain drugs, such as thiazide diuretics, and occupational exposure to toxins, such as polycyclic aromatic hydrocarbons (in coke oven workers), trichloroethylene, and perchloroethylene (in dry cleaning employees), are associated with an increased risk of RCC. However, no firm data have established a link between these drugs/toxins and RCC. Acquired cystic disease of the kidney, occurring in 80% to 95% of patients undergoing hemodialysis and 30% to 45% of those undergoing peritoneal dialysis, predisposes to RCC. These patients have a 5% to 30% likelihood of developing RCC, typically papillary in type, and approximately 15% of those who do develop RCC will present with metastatic disease.

In 1997, a new classification of renal epithelial tumors was adopted that established distinct subtypes based on morphology, genetic features, and cell of origin [5, 6] (Fig. 1). Conventional (clear cell) RCC comprises 65%