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Original Article

Persistent cough as a paraneoplastic presenting symptom in six patients with renal cell carcinoma

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Abstract *Objective:* With today's modern imaging modalities, patients diagnosed with renal cell carcinoma (RCC) rarely present symptomatically. In some cases, however, they can develop paraneoplastic syndromes with associated symptoms. To date, only three cases of RCC presenting with chronic dry cough have been reported. We describe six patients who presented with cough that improved following radical nephrectomy.

Methods: A retrospective review of patients undergoing partial or radical nephrectomy for renal masses between January 2015 and March 2016 was performed, and patients presenting with a cough were examined.

Results: Six patients presented with chronic cough and were discovered to have a large renal mass. Postoperative spontaneous resolution of cough was noted in all but one patient, in whom coughing was reduced and limited to the mornings. Cough duration ranged from 3 months to just over a year. All patients were treated with radical nephrectomy, which was cytoreductive in four patients. Average tumor size was 10.9 cm (SD = 2.2 cm). Five of the tumors had clear cell pathology, and every tumor was Fuhrman grade IV, unifocal, and demonstrated necrosis. Sarcomatoid features were reported in four of the tumors.

Conclusion: Our study presents the largest series of patients with RCC who presented with a chronic cough that was significantly improved following radical nephrectomy. We believe the cause of cough is multifactorial and further investigation is needed to clearly elucidate the etiology.

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1. Introduction

Renal cell carcinoma (RCC) is often asymptomatic, with an increasing number of patients being diagnosed incidentally thanks in large part to increased utilization of abdominal imaging [1]. When the disease does present symptomatically, however, RCC has variable clinical symptoms, commonly including hematuria, flank pain, fever, and weight loss. It is estimated that 10%–40% of patients develop paraneoplastic syndromes, including metabolic, hepatic, and hematologic syndromes [2]. Although the lungs are a common site of metastasis in patients with RCC, respiratory paraneoplastic syndromes are rare, with only three cases of RCC presenting with cough having been reported in the literature [3–5]. No clear explanation for these coughs has been elucidated; however, mass effect causing diaphragmatic irritation as well as paraneoplastic cytokines or growth factors have been hypothesized as possible causes. We present six patients, all of whom presented with cough that improved following radical nephrectomy.

2. Materials and methods

Following Institutional Review Board approval, data from patients undergoing partial or radical nephrectomy for renal masses between January 2015 and March 2016 from a high volume tertiary care center were prospectively collected. Patient demographics, presenting symptoms, preoperative lab values, surgical approach (open vs. laparoscopic), laterality, tumor pathology (size, histology, Fuhrman grade, pathologic stage, histological features, and focality), and postoperative follow-up were evaluated. Patients under the age of 18 and those with no history of cough were excluded. All patients had more than 3 months of postoperative surveillance.

Descriptive statistics are presented as counts and percentages for categorical variables and as means and standard deviations (SD) for continuous variables. All calculations were performed using SPSS, v24.0 (IBM, Chicago, IL, USA).

3. Results

3.1. Patient and disease characteristics

Six patients all presenting with a chief complaint of chronic dry cough and subsequently found to have large renal mass were identified. Postoperative spontaneous resolution of cough was noted in all but one patient, in whom coughing persisted but was significantly reduced and limited only to the mornings.

Baseline patient and disease characteristics are presented in Table 1. Mean age was 53.3 years (SD = 8.1 years), and five of the patients were male. Only one patient presented with flank pain and fever; the remaining patients reported weight loss averaging 4.8 kg (SD = 2.9 pounds). Cough duration ranged from 3 months to just over a year. Workup for cough included a CT scan of the chest and abdomen in five of the patients, which revealed a renal mass in each case; the final patient had been taking prednisone

Table 1 Baseline patient and disease characteristics.

Characteristics	Values
Age (years)^a	53.3 ± 8.1
Gender, N (%)	
Male	5 (83)
Female	1 (17)
Presenting symptoms^b	
Flank pain	1 (17)
Fever	1 (17)
Weight loss	5 (83)
Cough	6 (100)
Weight loss (kg)^a	10.5 ± 6.4
Duration of cough (month)^a	5.6 (4.1)
Nephrectomy type^b	
Radical	6 (100)
Cytoreductive	4 (67)
Surgical approach^b	
Open	1 (17)
Laparoscopic	5 (83)
Preoperative lab values^a	
Hemoglobin (g/L)	101 ± 19
Total serum calcium (mg/L)	97 ± 8
Alkaline phosphatase (U/L)	145.0 ± 69.5
Follow-up (months)^a	7.8 ± 3.4

^a Values are presented as mean ± SD.

^b Values are presented as N (%).

intermittently for several months, and his mass was not discovered until he presented with flank pain and fever.

All patients were treated with radical nephrectomy, and the operation was cytoreductive in four cases. Two patients had pulmonary nodules concerning for metastasis at the time of nephrectomy, one patient had mediastinal adenopathy, and another patient had periaortic adenopathy. Each nephrectomy began laparoscopically, but one needed to be converted to open following an intraoperative complication of hemorrhage leading to hypotension.

Table 2 summarizes tumor characteristics found on surgical pathology. Average tumor size was 10.9 cm (SD = 2.2 cm). Fig. 1 shows preoperative CT scans for each patient. Tumors were clear cell in five of the cases; one was unclassified due to mixed morphologic and immunohistochemical features. Every tumor was Fuhrman grade IV, unifocal, and demonstrated necrosis. Sarcomatoid features were observed in four of the tumors.

3.2. Follow-up

The average follow-up time was 7.8 months (SD = 3.4 months). Five out of six patients remain completely free of cough to date. Two of the patients are recovering well and now on surveillance, with no evidence of local recurrence or metastasis. They will continue to receive yearly imaging of the chest, abdomen, and pelvis.

In one patient, two new lesions, sized 2 mm and 6 mm, were seen in an MRI of the brain 4 months after nephrectomy. He underwent stereotactic radiation to his brain as well as whole brain radiation therapy. He is currently undergoing chemotherapy with axitinib for his metastatic RCC. A recent CT scan showed a decrease in lung and pleural-

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