Primary Renal Carcinoid Tumor: Report of Two Cases

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ABSTRACT

Introduction: Primary renal carcinoid tumors are a rare subset of neuroendocrine tumors arising in the kidneys. Although carcinoid syndrome has occasionally been described, most patients are asymptomatic at presentation.

Case Presentations: We present 2 cases of primary renal carcinoid tumor and describe the workup, immunohistochemical analysis, treatment, and surveillance of each female patient. The first patient was found to have a renal mass on imaging during a workup of chronic abdominal pain and subsequently underwent a robotic radical nephrectomy. The second patient was found to have an incidental renal mass on imaging and subsequently underwent renal biopsy, followed by robot-assisted laparoscopic partial nephrectomy. In both cases, a gallium dotatate Ga 68-enhanced positron emission tomography/computed tomography scan was used to further assess disease burden.

Discussion: This report describes 2 cases of primary renal carcinoid tumor with unique presentations and management in our regional health care system. Because primary renal carcinoid tumors are quite uncommon, there are no clear established guidelines on preoperative imaging or posttreatment surveillance in patients with these tumors. There remains a large amount of variability in the diagnosis, workup, immunohistochemical analysis, treatment, and surveillance of patients with primary renal carcinoid tumors. As we learn more about this disease, we hope to optimize patient outcomes and standardize pretreatment workup and posttreatment surveillance.

INTRODUCTION

Carcinoid tumors are a rare subset of neuroendocrine tumors (NETs), with 38 new cases diagnosed per 1 million individuals in the US each year, the majority of which are symptomatic.\(^1,2\) These tumors most commonly arise in the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%).\(^2\) Carcinoid tumors are rarely found in the retroperitoneum. Renal carcinoid tumors are well-differentiated primary NETs arising in the kidneys.

Although carcinoid syndrome has occasionally been described, most patients with carcinoid tumors are asymptomatic at presentation. Carcinoid syndrome occurs as a result of excessive serotonin production and release by the tumor, typically in patients with liver metastases. Major symptoms of carcinoid syndrome include facial flushing, diarrhea, marked changes in blood pressure (usually hypotension), malnutrition, and wheezing.\(^2\) The pathophysiology and risk factors associated with renal carcinoid tumors remain poorly understood. We present 2 cases of primary renal carcinoid tumor and describe the workup, immunohistochemical analysis, treatment, and surveillance of each patient.

CASE PRESENTATIONS

Case 1

A 58-year-old woman with a history of inflammatory bowel disease, hyperlipidemia, and prediabetes presented with complaints of vague, right-sided abdominal pain for roughly 1 year, as well as 2 isolated episodes of gross hematuria. Results of an abdominal ultrasonogram revealed an 8-cm, right upper pole renal mass. An 8-cm tumor with calcifications and areas of heterogeneity was confirmed on a computed tomography (CT) scan, in addition to regional lymphadenopathy, which was suspicious for tumor spread (Figure 1). The patient denied any history of weight loss or bone pain. The result of magnetic resonance venography was normal, showing no renal vein involvement, and CT scans of the chest and pelvis did not demonstrate any evidence of distant disease.

The patient was taken to the operating room and underwent a robotic right radical nephrectomy and retroperitoneal lymphadenectomy. The specimen was analyzed and found to be an 8-cm, circumscribed, hemorrhagic tumor with cystic degeneration. Pathologic findings revealed a well-differentiated renal NET extending into the collecting system, with 4 of 5 hilar and paracaval/
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retrocaval resected lymph nodes found to be involved by tumor, without any renal vein or perirenal fat involvement (pT2aN1M0). The surgical margins were negative for cancer.

The patient was doing well at her 6-month follow-up appointment. Urine levels of 5-hydroxyindoleacetic acid (5-HIAA) and serum serotonin levels were found to be normal, and the serum chromogranin A level was 169 ng/mL (normal < 95 ng/mL). Preoperative tumor markers were not obtained because we were unaware of her diagnosis until the histologic findings revealed a carcinoid tumor.

She underwent a gallium dotatate Ga 68 (68Ga)-enhanced positron emission tomography (PET/CT) scan 8 months postoperatively to evaluate for residual and/or metastatic disease. Gallium dotatate Ga 68 is a specific radiotracer in PET imaging that is used to evaluate NETs. The scan revealed a 0.7-cm, mildly hypermetabolic (peak standardized uptake value = 3.1) retroperitoneal lymph node in the aortocaval region, which was suspicious for possible recurrence. This lesion was too small for a percutaneous biopsy, and the patient will undergo a follow-up 68Ga-enhanced PET/CT scan in 3 months. Table 1 presents a timeline of this case.

Case 2

A 28-year-old woman with no remarkable medical history was seen for evaluation of a subjective lump on the left side of her neck in the supraclavicular area. Results of CT scans of the neck and chest were unrevealing; however, an incidental lesion was noted in the right lobe of her liver. A magnetic resonance image of her liver revealed an 8-mm, right hepatic lobe lesion consistent with a hemangioma, a 4.5-cm lesion in the left hepatic lobe consistent with benign focal nodular hyperplasia, and a 4.4-cm, enhancing right interpolar renal mass without any regional lymphadenopathy. A CT scan confirmed the presence of the endophytic mass, which was noted to be abutting the renal collecting system (Figure 2). A renal biopsy specimen was obtained, which revealed a well-differentiated NET. The patient denied any symptoms suggestive of carcinoid syndrome. Her tumor markers were checked, and her preoperative serum chromogranin A level was 799 ng/mL, and 24-hour urine 5-HIAA levels were mildly elevated at 6.5 mg (normal < 6 mg).

A 68Ga-enhanced PET/CT scan confirmed a right renal mass with increased activity (maximum standardized uptake value = 58.8). The scan otherwise showed no evidence of metastatic disease, including of the previously mentioned liver lesions.

Given these findings, the patient was taken to the operating room and underwent a right-sided robot-assisted laparoscopic partial nephrectomy, with a warm ischemia time of 25 minutes. Pathologic findings (Figure 3) revealed a 4.4-cm, well-differentiated, low-grade NET with lymphovascular invasion; a mitotic count less than 2 of 10 per high-power field [HPF]; a Ki-67

<table>
<thead>
<tr>
<th>Date</th>
<th>Summaries from initial and follow-up visits</th>
<th>Diagnostic testing</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/8/2018</td>
<td>Presented to family medicine physician with right-sided abdominal pain</td>
<td>Right renal mass (8 cm) identified on ultrasonogram</td>
<td>Right renal mass confirmed on CT</td>
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<tr>
<td>8/31/2018</td>
<td></td>
<td>Postsurgical pathologic findings revealed a well-differentiated renal NET extending into the collecting system</td>
<td>Surgical resection (robotic radical nephrectomy)</td>
</tr>
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<td>9/13/2018</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>11/6/2018</td>
<td></td>
<td>Surveillance gallium dotatate Ga 68 (68Ga)-enhanced PET/CT scan revealed a 0.7-cm, mildly hypermetabolic retroperitoneal lymph node in aortocaval region, which was suspicious for possible recurrence</td>
<td>Recommended to undergo a follow-up 68Ga-enhanced PET/CT scan in 3 mo</td>
</tr>
<tr>
<td>7/2/2019</td>
<td></td>
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CT = computed tomography; NET = neuroendocrine tumor; PET = positron emission tomography.
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Index less than 2% (World Health Organization grade 1); and negative surgical margins (pT1bNx).

One month postoperatively, the patient’s chromogranin A level normalized to 50 ng/mL, and 24-hour urine 5-HIAA levels normalized to 3.2 mg. She will receive her first surveillance imaging at 6 months postoperatively. Table 2 presents a timeline of this case.

DISCUSSION

The diagnosis of a primary renal carcinoid tumor is typically achieved using a multimodal approach, including biochemical testing and imaging, with histologic analysis with immunohistochemical staining remaining the gold standard for confirmation. Chromogranin A remains the most sensitive serum test available, and 24-hour urine 5-HIAA levels are elevated in 50% of cases. Reported adverse prognostic features include age older than 40 years, tumor size larger than 4 cm, mitotic count above 1 of 10 per HPF, and metastases at initial diagnosis.

A study of 11 renal NETs used next-generation sequencing to identify genetic mutations and found a highly variable mutation profile. All tumors were positive for synaptophysin, and 73% expressed chromogranin A. In addition, 73% showed cytoplasmic positivity of CD99, whereas only 27% were positive for CD56. Multiple other genetic aberrations were noted as well.

Another study of 6 patients with well-differentiated NETs found that cases of lymph node involvement or distant metastases had high mitotic counts (> 2 of 10 per HPF) and higher Ki-67 proliferative indexes of primary lesions. Of note, Ki-67 protein expression is associated with cellular proliferation. In our case 1, the tumor stained positive for pancytokeratin, synaptophysin, CD56, and CD10, and it had a low Ki-67 proliferative index rate (< 10% of tumor). There was presence of lymphovascular invasion. The tumor stained negative for CK7, CK20, PAX8, GATA3, EMA, and CEA. In case 2, the histologic analysis of the tumor (Figure 3) showed a low mitotic count of less than 2 of 10 per HPF and a low Ki-67 index less than 2%, and showed immunostaining positivity for CD31 highlighting endothelial cells, supporting the presence of lymphovascular invasion. Neither patient’s tumor showed evidence of necrosis or sarcomatoid/rhabdoid features. The immunohistochemical findings for primary renal carcinoid tumors remain highly variable both in staining patterns and pathologic reports.

The primary treatment of localized renal carcinoid tumors is excision either by radical or partial nephrectomy. Much like in the renal cell carcinoma cohorts, partial nephrectomy has gained popularity when technically feasible in hopes of maximizing postoperative renal function. The tumor in case 1 was not amenable to partial nephrectomy, and furthermore the lymphadenopathy on preoperative images suggested more advanced disease; thus, an approach involving radical nephrectomy and regional lymphadenectomy was used. Lymph node metastasis has been reported in one-third of cases of renal carcinoid tumor. In contrast to this, the tumor in case 2, although endophytic, was safely excised by performing a partial nephrectomy, with negative surgical margins. Once renal carcinoid tumors become metastatic, treatment can include somatostatin analogs such as octreotide, pasireotide, and

Table 2. Timeline of case 2

<table>
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</thead>
<tbody>
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<td>11/28/2018</td>
<td>Seen for evaluation of a subjective lump on the left side of her neck</td>
<td>Right renal mass (4.4 cm) identified on magnetic resonance images after CT scans</td>
<td>Surgical resection (robot-assisted laparoscopic</td>
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<td></td>
<td></td>
<td>of the neck and chest revealed an incidental lesion in the right hepatic lobe</td>
<td>partial nephrectomy)</td>
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<td>12/31/2018</td>
<td>Renal biopsy specimen revealed a well-differentiated NET</td>
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<tr>
<td>1/22/2019</td>
<td>Gallium dotatate Ga 68 (68Ga)-enhanced PET/CT scan confirmed a right renal mass</td>
<td>Surgical resection (robot-assisted</td>
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<tr>
<td></td>
<td>with increased activity but showed no evidence of metastatic disease</td>
<td>(laparoscopic partial nephrectomy)</td>
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<tr>
<td>2/28/2019</td>
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<td></td>
<td></td>
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<tr>
<td>4/5/2019</td>
<td>Postoperative biochemical test results normalized</td>
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lanreotide, as well as everolimus. It is important to note, however, that long-term survival outcomes have not been well described given the rarity of this disease. More prospective trials are needed to determine the optimal treatment in advanced disease.

Because primary renal carcinoid tumors are quite uncommon, there are no clear established guidelines on preoperative imaging or posttreatment surveillance in patients with these tumors. Radiolabeled gallium Ga 68 has been shown to be useful in disease detection using 68Ga-enhanced PET/CT, with improved sensitivity compared with CT, magnetic resonance imaging, or 18-fluoride fluorodeoxyglucose PET/CT, as well as useful in treatment through peptide-receptor radionuclide therapy. Not only can 68Ga-enhanced PET/CT be used to detect NETs, but it has also been shown to be an accurate tool for assessing total disease burden, stratifying each patient’s risk status, and assessing response to treatment, as well as posttreatment surveillance. Because we were unaware that the patient in case 1 had a carcinoid tumor before radical nephrectomy, she did not undergo preoperative imaging with this tool. She did, however, undergo a surveillance 68Ga-enhanced PET/CT scan postoperatively, which identified a small, mildly hypermetabolic lymph node. Given the biopsy-proven renal carcinoid tumor in case 2, that patient underwent a preoperative 68Ga-enhanced PET/CT scan, which only showed increased activity in her primary renal mass. Her tumor markers normalized postoperatively, and she will undergo serial surveillance imaging using 68Ga-enhanced PET/CT, the first of which will be obtained 6 months postoperatively.

CONCLUSION

Primary renal carcinoid tumors are rare. This report describes 2 cases with unique presentations and management in our regional health care system. There remains a large amount of variability in the diagnosis, workup, immunohistochemical analysis, treatment, and surveillance of patients with primary renal carcinoid tumors. Novel therapies using radiolabeled gallium Ga 68 in both imaging and treatment modalities are emerging. As we learn more about this disease and mimic treatment trends in gastrointestinal NETs, we hope to optimize patient outcomes and standardize pretreatment workup and posttreatment surveillance.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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How to Cite this Article


References


In Reverse

It is no exaggeration to say that the composition of the blood is determined not by what the mouth ingests but by what the kidneys keep; they are the master chemists of our internal environment, which, so to speak, they synthesize in reverse.

— Horner William Smith, ScD, 1895-1962, American physiologist and advocate for science