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Primary renal carcinoid tumor: A radiologic review

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Carcinoid tumor is the classic famous anonym of neuroendocrine neoplasms. Primary renal carcinoid tumors are extremely rare, first described by Resnick and colleagues in 1966, with fewer than a total of 100 cases reported in the literature. Thus, given the paucity of cases, the clinical and histological behavior is not well understood, impairing the ability to predict prognosis. Computed tomography and (occasionally) octreotide studies are used in the diagnosis and followup of these rare entites. A review of 85 cases in the literature shows that no distinctive imaging features differentiate them from other primary renal masses. The lesions tend to demonstrate a hypodense appearance and do not usually enhance in the arterial phases, but can occasionally calcify. Octreotide scans do not seem to help in the diagnosis; however, they are more commonly used in the postoperative followup. In addition, we report a new case of primary renal carcinoid in a horseshoe kidney.

Case report

40-year-old male initially presented to a community hospital with a 20-lb weight loss over a few months. In retrospect, the patient recalled mild left-flank discomfort and fatigue, but denied any hematuria. Blood work revealed an elevated serum glucose, and he was diagnosed with type 2 diabetes. Further workup included ultrasound, which revealed a tumor in his retroperitoneum abutting a left moiety of a horseshoe kidney.

The patient's past medical history was significant for recently diagnosed type 2 diabetes and a knee ligamentous injury at the age of 14. Medications included metformin, diamicron, ventolin, and symbicort. His family history consisted of a maternal grandfather requiring a nephrectomy; the patient was unsure of the cause. There was no known family history of renal-cell carcinoma.

Physical examination was unremarkable, with no flank or abdominal pain. All biochemical and hematological workup was normal, including CBC, LFTs, creatinine, and calcium.

Imaging findings

CT of the abdomen and pelvis, done in the portal venous phase, demonstrated a solid, hypodense, 4.5-cm renal mass containing calcifications, located in the posterior aspect of the medial portion of the left renal moiety of the horseshoe kidney (Fig. 1). The mass did not enhance strongly in the venous phase, and there was no apparent metastatic disease. Subsequent MRI attempted to further characterize the renal mass; it revealed an enhancing left renal upper pole mass measuring approximately 4.1 x 3.8 cm, which demon-

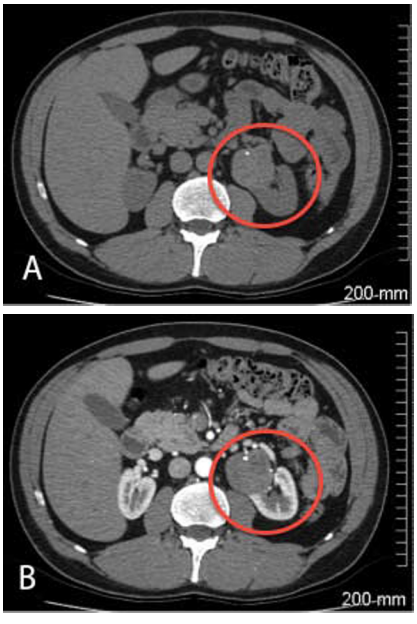

Figure 1. Computed tomography imaging of axial slices, unenhanced (A) and enhanced (B), showing left renal carcinoid (circled in red) in horseshoe kidney.

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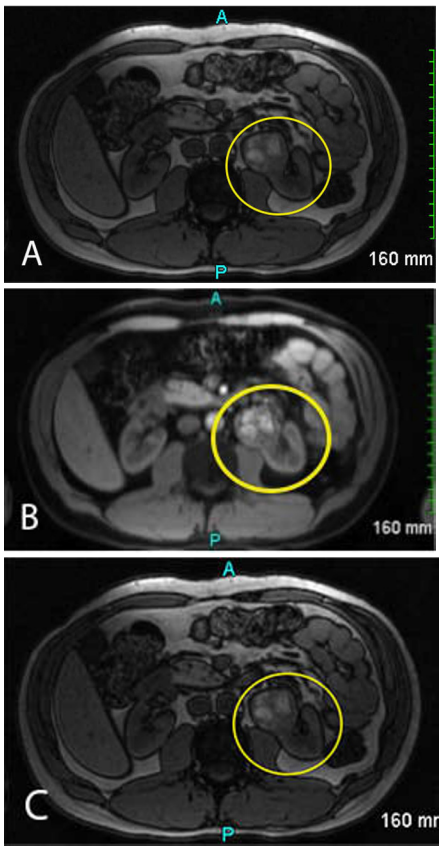

Figure 2. MRI axial T1 Dixon VIBE out of phase (A), T1 VIBE gadolinium-enhanced fat-saturated (B), and T1 FLASH gadolinium-enhanced fat-saturated sequences (C) showing left renal mass (circled in yellow) in a horsehoe kidney.

strated a heterogeneous signal intensity on both T1 and T2-weighted images with areas of bright signal on T1-weighted images, likely due to intralesional hemorrhage (Fig. 2). Although the tumor abutted the psoas muscle, it did not appear to invade it.

Management

A pre-operative chest radiograph was negative for metastatic disease. The patient was taken to the operating room and underwent an uncomplicated partial left nephrectomy. Intra-operatively, it was obvious that the mass did not invade the psoas muscle. Pathology revealed a well-differentiated neuroendocrine tumor, its histology compatible with carcinoid. Numerous immunostains were performed. The neoplastic cells were negative for inhibin, TTF-1, keratin 903, carbonic anhydrase IX, PAX-2, RCC antigen, S-100, CD10, CK7, and CK20. The tumor cells were strongly and diffusely positive for neuroendocrine markers, including synaptophysin, chromogranin A, and CD56. The cells were also positive for vimentin and weakly for racemase (AMACR). The proliferation index, as demonstrated by Ki-67 staining, was low, at 1-2%.

Followup

Postoperative CT thorax, octreotide study, endoscopy, and colonoscopy were all negative, with no source of gastrointestinal tumor identified. The patient is now approximately two years post surgery, with no evidence of local recurrence or metastatic disease.

Discussion

Etiology and demographics

Carcinoid tumor is the classic famous anonym of neuroendocrine neoplasms, first described in 1888 by Lubarsch (1). It gained its name from the earlier description of benign behavior of the lesion despite its malignant appearance under microscopy (2). It arises from a wide variety of tissues and organs, most commonly from specialized endocrine cells in the gastrointestinal and respiratory tracts, with prevalence values of 66.9% and 24.5%, respectively (3). The tumors produce hormones and protein products associated with specific clinical symptoms, and their malignant potential varies by location and cell type. Primary renal carcinoid tumors are extremely rare; they were first described by Resnick and colleagues in 1966 (4), with fewer than a total of 100 cases reported in the literature (5, 6). Thus, given the paucity of cases, the clinical and histological behavior is not well understood, impairing the ability to predict prognosis.

Carcinoid tumors arise from neuroendocrine cells and are believed to originate from enterochromafin or amine precursors and decarboxylation cells with malignant potential; however, neuroendocrine cells are not identified in the kidney or renal pelvis (7-10). Although renal carcinoid tumors exhibit morphologic and immunohistochemical features consistent with a hindgut neuroendocrine phenotype, the precise pathogenesis is controversial (11). Several hypotheses have been proposed, on the basis that these tumors arise from interspersed neuroendocrine cells associated with acquired and/or congenital abnormalities. The first hypothesis suggests that chronic inflammation induces metaplasia of the pyelocalciceal urothelium (12-14). The second suggests that they are metastases from an unknown primary (15). The third is that the neural crest or pancreatic cells have been misplaced or abnormally migrated during embryogenesis (14, 16). The fourth suggests concurrent congenital renal abnormalities (17, 18). And the last hypothesis suggests activation of gene sequences in multipotent primitive stem cells (5, 19, 20-28).

Methods

We performed an extensive literature search for all reported renal primary carcinoid tumors. In total, we reviewed 85 cases, with one unpublished case from our institution. We evaluated demographical, clinical, histopathological, and prognostic data, with a focus on radiologic findings.

Demographics

Of the 85 cases, 50 were males (59%) and 35 females (41%), with ages ranging from 12 to 75. The average age of diagnosis was 47.7 years, and the median age was 49 years. Forty-eight tumors were right-sided, and 37 were left-sided. Of the 85 cases, 50 were between 0-4 cm, 34 cases were more than 4 cm, and one size was not specified.

Several cases in the literature have reported coexisting renal anomalies such as horseshoe kidney and teratomas, suggesting that this disease may perhaps be more common

when there are predisposing embryological factors (17, 5). Of the 85 cases, 19 were in horseshoe kidneys (22.3%) and 10 in teratomas (11.8%). Of those not in horseshoe kidneys, 51 of 66 cases were in the renal parenchyma (77.3%), 3 were in the renal pelvis (4.5%), 3 in the renal hilum (4.5%), and 8 were not specified.

Presentation

Patients with carcinoid tumors usually present with nonspecific symptoms related to the mass such as pain, obstruction, a palpable abnormality, or hematuria. Rarely are symptoms related to hormone production and result in carcinoid syndrome, first described in 1957 by Pernow and Waldenstrom (29), and characterized by skin flushing and telangiectasia, diarrhea, abdominal pain, cardiac valvular lesions, and bronchoconstriction. Carcinoid syndrome was found in only 4 of the 85 cases.

These tumors are often discovered incidentally, as in 26 of the cases. Thirty-nine patients presented with metastatic disease: 28 with metastases in lymph nodes, 8 in bones, 3 in lungs, 1 in the renal bed, 1 in the bowel, 1 in the spleen, 1 in the thyroid, and 1 in the breast.

Diagnosis

Initial evaluation often includes biochemical testing with urinary 5-HIAA, tumor localization with CT, and pre- or post-operative octreotide scans. Diagnostic workup practices were extremely varied in the cases analyzed, likely since the tumor is rare and there is no standard, or common, practice.

Urinary 5HIAA

The measurement of serotonin metabolite 5-HIAA in 24-hour urine collection has been historically used to confirm the diagnosis and subsequently to monitor patients with metastatic carcinoid tumors (30). It was only occasionally ordered in the renal carcinoid cases reviewed. Urinary 5-HIAA is not considered sensitive or specific for carcinoid syndrome, as it may be elevated in other conditions such as tropical sprue, celiac disease, Whipple's disease, and small bowel obstructions (31).

Octreotide scintigraphy

Octreotide scintigraphy has been introduced into the radiological armamentarium as a sensitive imaging modality for the diagnosis and staging of carcinoid tumors, particularly gastrointestinal carcinoid. Radioactive octreotide is a synthetic and slowly degraded somatostatin analog that binds to somatostatin receptors. Of the primary carcinoids and metastases of gastrointestinal and bronchial origin, more than 85% have high-affinity receptors for somatostatin (32, 33). Thus, the reported sensitivity of this method in detecting carcinoid tumors has been reported to be greater than 85% (32, 34, 35).

Nevertheless, it is not routinely used in the renal carcinoid pre-operative workup. More commonly, although still not performed often, the octreotide scan is used for post-resection monitoring (32). In fewer than 10 cases in the literature were octreotide studies performed, 60% of which were 1 to 2 months after surgical resection (and were negative).

Thus, given the paucity of cases, octreotide sensitivity is not well established. Although it has a high stated sensitivity in detecting gastrointestinal tumors, relatively little is known about renal carcinoids such as the somatostatin receptor prevalence. Further, a known limitation of scintigraphy with octreotide to evaluate primary kidney carcinoids is that the normal renal uptake of tracer material may obscure a suspicious lesion (36).

CT is most often used for postoperative surveillance, but it occasionally lacks the accuracy needed for postoperative staging and monitoring. Long-term followup is suggested, as new metastases have been reported as long as 7 years after resection (6). Thus, the octreotide scan could potentially serve as an adjunct for staging and surveillance of metastatic disease.

Radiologic imaging findings

Of the 85 cases, only 29% were hyperdense; the remainders were either hypodense (55%) or not specified (15%). Of the enhanced cases, only 18% demonstrated marked enhancement, and 14% showed mild enhancement. Calcifications were a common feature in one third of the cases.

Differential diagnosis

Thus, no specific radiologic feature on CT or MRI defines renal carcinoid, making the differentiation between renal carcinoid and renal-cell carcinoma unreliable on imaging alone (37). These stated radiological findings are most commonly seen with renal-cell carcinoma, and features should prompt consideration of renal-carcinoid tumors in the differential diagnosis, especially in the presence of the rare hormone-producing syndromes.

Pathology

Renal carcinoids typically exhibit the classic features of carcinoids found in other sites (38). They are well demarcated from adjacent normal parenchyma. Microscopically, cells are round or polygonal and are characterized by tightly packed cords and trabeculae of neoplastic cells appearing eosinophilic with a granular cytoplasm (38, 39). Trebecular/gyriform, insular, glandular, solid, and mixed architectural patterns are seen. Nuclei are round and contain fine stippled chromatin (39). They have a ribbonlike appearance, with minimal stroma (often composed of fibrous tissue). Calcifications are present in around 25% of cases, and frequent mitosis (42 per 10 HPFs) are characteristically absent (39). Microscopic foci of necrosis and focal areas of cytologic atypia are not uncommon (38).

The ability to diagnose these tumors has greatly increased since the advent of immunohistochemical staining. Carcinoid tumors stain positive for cytokeratin, chromogranin, synaptophysin, gremileus, and neuron-specific enolase, which serve to distinguish these tumors from renal-cell carcinoma (5, 40).

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