Case Report

Neuroendocrine tumor of the kidney: Diagnostic challenge and successful therapy

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Abstract

The management of gastrointestinal and pancreatic (GEP) neuroendocrine tumors (NETs) has evolved over the recent decade. Primary renal NETs are extremely rare as neuroendocrine cells are not recognized in the normal renal parenchyma. We report a case of primary renal NET characterized by the initial diagnostic challenges. Recurrent and metastatic disease was managed along the lines of management of GEP-NETs, leading to prolonged progression-free survival.

Keywords: Kidney, management, neuroendocrine tumors

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INTRODUCTION

Neuroendocrine tumors (NETs) are a group of uncommon conditions arising mostly in the gastrointestinal tract, pancreas, and lungs. Examples of other rare sites include thyroid and parathyroid glands and the thymus. Regardless of the anatomical site of origin, NETs share certain basic histopathological features that are distinct from those of conventional epithelial cancers. NETs are classified according to the differentiation describing the extent of resemblance to the normal cellular counterpart guided by mitotic rate and Ki-67 expression. Thus, NETs may be well differentiated (WD) or poorly differentiated.[1] Pheochromocytoma and neuroblastoma are distinct forms of NETs arising from the adrenal gland medulla. However, primary WD-NETs of the kidney are very rare because neuroendocrine cells are not found within normal renal parenchyma, and thus, the pathogenesis of renal NETs remains unexplained.[2] Here, we report a case of primary renal WD-NET describing the initial histopathological challenges. Subsequent development of recurrent and metastatic disease was managed by multimodality therapies, leading to disease response and prolonged progression-free survival.

CASE REPORT

A 20-year-old gentleman presented to his local hospital in 2004 and was found to have an isolated left kidney mass. Image-guided biopsy was reported as Wilms's tumor (WT). Treatment at the local hospital was limited to radiofrequency ablation (RFA) of the tumor. In November 2010, he presented to the same hospital with gastrointestinal symptoms. A computed tomography (CT) scan showed one lesion in the left kidney and five others in the liver. Biopsy of one of the liver lesions was reported as WD-NET.

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He was first seen in the oncology clinic at our hospital in February 2011. CT scan confirmed the above radiological findings. The patient did not exhibit any systemic carcinoid symptoms. Serum chromogranin-A and urinary 5HIAA levels were within normal range.

The renal biopsy obtained in 2004 from the original left kidney tumor was reviewed at our institution. The histological features and the immunoprofile were interpreted to be consistent with WD-NET.

The left kidney lesion and the five liver lesions were resected surgically in May 2011. Histological examination confirmed the diagnosis of WD-NET in all specimens. Morphologically, the kidney lesion exhibited trabecular growth pattern with conspicuous intervening fibrotic stroma and focal attempt to form rosette-like structures. The tumor cells were monomorphic round to polygonal with granular amphophilic-to-eosinophilic cytoplasm and uniform round nuclei with characteristic finely stippled chromatin. The tumor cells were positive for pankeratin, CAM 5.2, NSE, synaptophysin, chromogranin, vimentin, PSAP, and CD56 but negative for PAX-8, CK7, CK20, CDX-2, PSA, napsin-A, TTF-1, renal cell carcinoma (RCC), CD10, and WT-1. Proliferation index (Ki-67) was expressed in 1% of tumor cells, and the mitotic rate was 1/10 HPF [Figure 1a-c].

The liver lesions revealed similar morphological features and to some extent equivalent immunoprofile but with vanished chromogranin expression and slightly increased Ki-67) of 3%. The mitotic rate was 8/10 HPF.

A routine follow-up CT scan in October 2011 confirmed recurrence in the left kidney remnant, right suprarenal gland, liver, and mesenteric lymph nodes [Figure 2]. Serum chromogranin-A and urinary 5HIAA levels remained within normal range. Monthly intramuscular 30 mg of long-acting octreotide was started. Sequential CT scans over the subsequent 7 years confirmed slow but sustained radiological partial response [Figure 2a-f]. Treatment was well tolerated with no reported side effects. The patient was last reviewed in a clinic in August 2018. He was fully active and enjoining a normal physical quality of life.

DISCUSSION

The diagnosis of NETs is based on classic histological features and the use of adjunct immunohistochemistry. This case illustrates that the misdiagnosis of NETs is possible in a nonspecialized setting where skills and resources are limited. The morphological differential diagnosis can be challenging in needle core biopsies as opposed to nephrectomy specimens and can include metanephric adenoma, renal oncocytoma, paraganglioma, papillary RCC, primitive neuroectodermal tumor, neuroblastoma, WT, and small cell carcinoma.[3] Other possible explanations for misdiagnosis include lack of suspicion for this entity, unusual renal site of presentation, limited biopsy material, and inadequate crucial ancillary diagnostic tools such as immunohistochemistry.

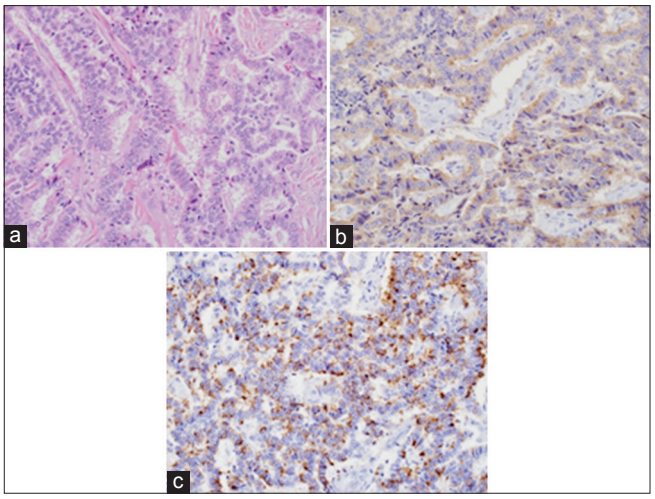

Figure 1: (a-c) Histological and immunohistochemical features of the resected kidney lesion. (a) Tumor with trabecular growth pattern (H and E, ×20). (b) Synaptophysin (immunohistochemistry). (c) Chromogranin (immunohistochemistry)

Renal WD-NETs are rare and have been primarily documented in the literature as case reports or short series of which the largest described 21 cases from five major institutions diagnosed between 1970 and 2006.[4] Only three cases of renal WD-NETs (and six small cell carcinoma) were identified at the University of Texas MD Anderson Cancer Center over 10 years.[5]

Our patient experienced disease relapse 6 years after the initial RFA therapy. It is not clear why this modality of treatment was applied at that time. The development of distant metastases in addition to the local recurrence indicates blood-borne dissemination. This is supported by the development of liver and other metastases within 5 months after apparently complete surgical debulking. Metastatic disease from WD gastrointestinal and pancreatic NETs is present in 40%–50% of the patients at initial diagnosis with increasing prevalence over time depending on initial disease stage.[6] It seems that renal WD-NETs have equally high propensity to metastasize. Certainly, Hansel *et al.* reported metastases in 12/13 cases of renal WD-NETs at the time of surgery.[4]

The rarity of primary renal NET opens the question of an occult NET metastasizing to the kidney. This is unlikely to

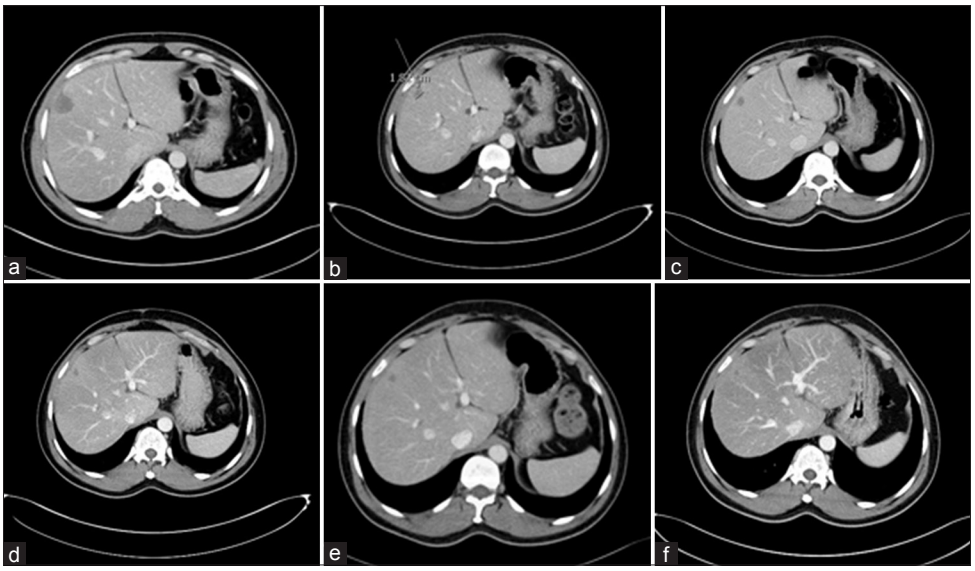

Figure 2: Serial computed tomography (a) metastatic liver lesion just before starting octreotide-LAR therapy in October 2011 (b-f) Subsequent computed tomography images over 82 months demonstrating continuous and maintained response. (b) August 2013, (c) August 2014, (d) August 2016, (e) July 2017, (f) August 2018

be the scenario in our case as there was a long disease-free interval between initial presentation and recurrence during which a presumed occult primary would have manifested. Immunohistochemistry has a limited role in determining the primary site of NETs, making it challenging to establish the site of origin. Applying site-specific markers such as CDX-2, PDX-1, and TTF-1 may be useful in certain scenarios. However, the sensitivity and specificity of these markers can be limited.[7]

Immunohistochemical examination confirmed CD56 expression in all resected renal and metastatic liver lesions. However, there was a lack of CD56 expression in the initial renal needle core biopsy, which could be related to handling and technical issues at the primary referring hospital. In addition, we noticed a loss of chromogranin expression in the metastatic liver lesion compared to the primary renal NET. This can be attributed to the loss of tumor antigenicity secondary to progression of tumor differentiation during metastasis.

Due to its rarity, there is no consensus on the standard treatment of metastatic renal WD-NETs. In addition, most of the literature reporting this condition did not describe details of systemic therapy. Octreotide LAR is a long-acting somatostatin analog. The PROMID trial randomized patients with midgut metastatic WD-NETs to either octreotide-LAR or placebo. Median time to tumor progression (TTP) was longer and rate of stable disease was more frequent with octreotide-LAR (14.3 vs. 6 months, hazard ratio = 0.34; 95% confidence interval, 0.20–0.59; $P = 0.000072$ and 66.7% vs. 37.2%, respectively).[8] Based on these data and in the absence of specific standard treatments for metastatic renal WD-NETs, our patient was started on octreotide-LAR, resulting in radiological response and very long TTP (82 + months). The patient continues to receive octreotide-LAR without any side effects and is enjoying an active life with excellent physical quality.

It is unfortunate that disease progression is almost inevitable sometime in the future, and thus, the question is, what will be the next line of therapy in that case? European and other guidelines are based on evidence obtained from trials and studies in patients with intestinal, pancreatic, and bronchial NETs.[6] It will be acceptable to apply these guidelines in patients with WD-NETs arising from other sites. Upon progression, considering the following systemic strategies will be appropriate: (1) inclusion in a clinical trial, (2) everolimus, (3) peptide receptor radionuclide therapy, (4) interferon-alpha, (5) sunitinib, and (6) chemotherapy. Local and locoregional treatments, when appropriate, can also be considered such as (1) surgical resection, (2) RFA, (3) transarterial chemoembolization, and (4) transarterial embolization. Liver transplantation is generally not recommended, but it may be an option for few selected cases in highly specialized centers. Liver transplantation is unlikely to be appropriate for our patient due to the presence of extrahepatic metastases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and

other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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