Well-differentiated neuroendocrine tumor of the right kidney: A case report

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Abstract. Neuroendocrine tumors (NETs) are tumors originating from neuroendocrine cells and peptidergic neurons. Primary renal well-differentiated NETs (WDNETs) are rare and only sporadic cases have been reported worldwide. In November 2021, a 45-year-old female patient was admitted to The Affiliated Hospital of Zunyi Medical University (Zunyi, China) with right-sided lumbago. Abdominal computed tomography revealed a 44x34x70-mm mass in the right kidney. Following a complete examination, a laparoscopic partial nephrectomy of the right kidney was performed under general anesthesia. The postoperative pathology indicated a well-differentiated NET of the right kidney. There was no tumor recurrence or metastasis during the 1-year follow-up period. WDNETs are rare, their clinical and imaging findings are not specific, and their diagnosis depends on immunohistochemical analysis. The degree of malignancy is low and the prognosis is positive. Surgical resection is often the first choice, and long-term follow-up is required.

Introduction

Neuroendocrine tumors (NETs) comprise a tumor class originating from neuroendocrine cells and peptidergic neurons, and are common in the respiratory and gastrointestinal tracts. Well-differentiated NETs (WDNETs) are a rare type of NET, comprising <1% of all cases (1,2). WDNETs have a better prognosis than neuroendocrine carcinoma, therefore, for patients with WDNETs and without metastases, surgical resection is the preferred approach. In the present study, a patient with a WDNET, also known as primary renal carcinoid tumor, was recently admitted to the Department of Urology, The Affiliated Hospital of Zunyi Medical University (Zunyi, China). Postoperative follow-up for 1 year indicated no tumor recurrence or metastasis. The present study retrospectively analyzed the patient's medical records, diagnosis and treatment process. This information was combined with an analysis of the literature, aiming to share the experience of diagnosis and treatment of WDNETs, and provide new strategies for patient follow-up.

Case report

A 45-year-old female patient was admitted to The Affiliated Hospital of Zunyi Medical University with right-sided lumbago in November 2021. By analyzing the patient's history, it was discovered that occasional right lumbago, accompanied by general fatigue, has been experienced for several months. There was no record of fever, bellyache, hematuria, frequent urination, hesitancy or loss of weight. The patient had previously undergone a total hysterectomy 5 years prior to admission and had no history of hypertension, diabetes, cancer or other relevant familial diseases. Following a physical examination, no abnormal signs were noted. No significant abnormalities were noted in the expression levels of chromogranin A (CGA) and in other biological functions on blood tests. Abdominal computed tomography (CT) in the venous phase demonstrated a well-circumscribed, slightly enhanced mass with an approximate size of 44x34x70 mm and a solid component; this mass was accompanied by sporadic fatty and calcified components, and was located in the right renal area. The left kidney function was normal (Fig. 1A and B). No evidence of distant or nodal metastases was present. Vascular examination indicated that the right renal arteries and the branch arteries were normal in shape without filling defects; the right renal vein and inferior vena cava were also normal. Additional examinations did not show any abnormalities. The clinical diagnosis was initially of a right renal paraganglioma (PPGL). A laparoscopic partial nephrectomy of the right kidney was performed under general anesthesia. During the operation, the tumor was discovered in the renal sinus, between the renal vein, renal artery and renal pelvis, and there was no vascular or lymphatic invasion. The renal artery was blocked with vascular blocking clips and the tumor was removed completely. Intraoperative blood pressure was within the normal range without significant fluctuation. After the operation, the tumor specimen was sent to the

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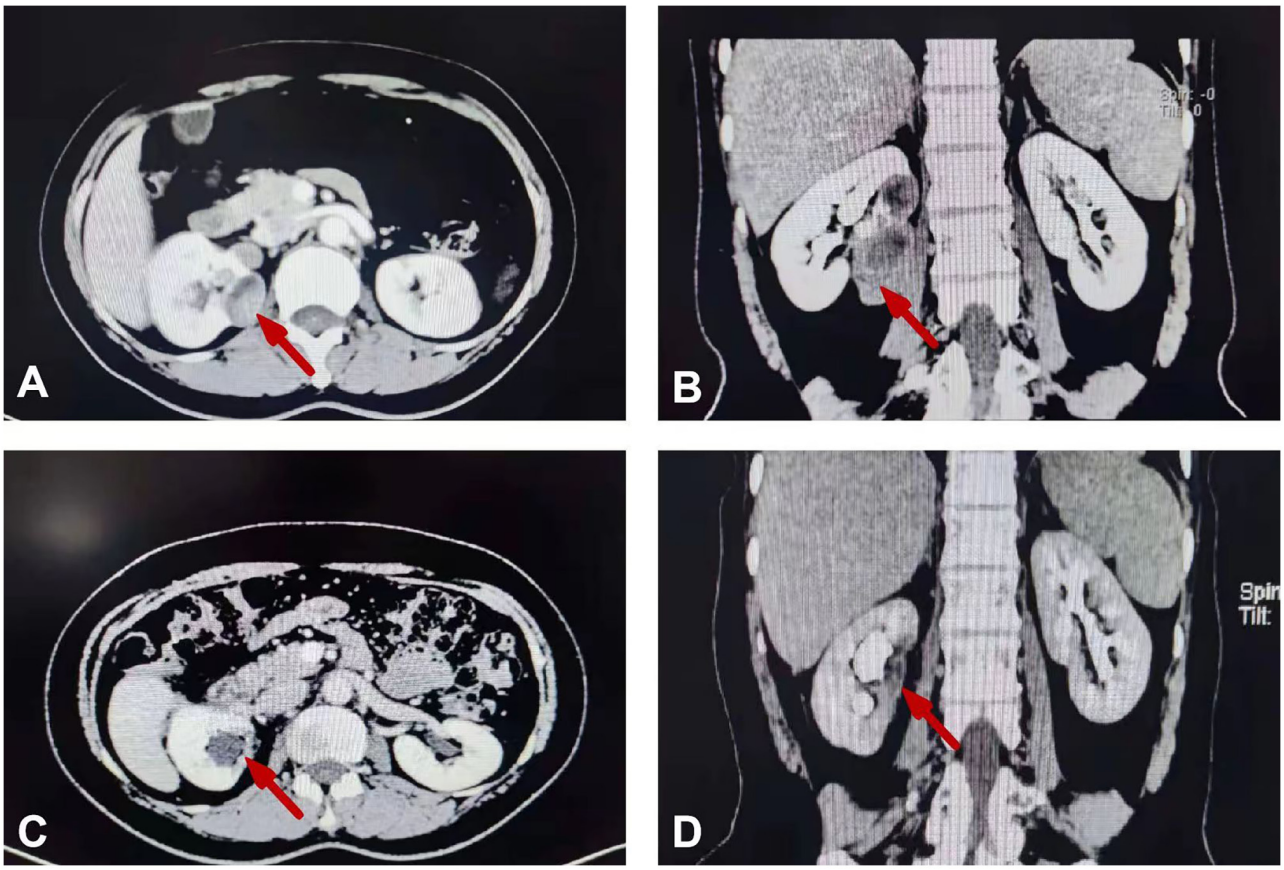

Figure 1. Results of abdominal computed tomography. (A) A well-circumscribed and slightly heterogeneous enhancing mass in the venous phase. The left kidney was normal. (B) The image demonstrated that the tumor was a 44x34x70-mm mass with a solid component, located in the right renal region and accompanied by sporadic fatty and calcified components. (C) At 1-year post-surgery, computed tomography indicated the absence of any residual tumor and mild hydronephrosis in the right kidney following partial nephrectomy. (D) The 3D reconstruction indicated that the tumor on the inside of the kidney was completely removed.

Department of Pathology. Gross examination of the tumor specimen indicated a solid mass of 40x30x70 mm, and the cut surfaces were gray with a complete capsule (Fig. 2). The tissue samples were fixed with 4% formaldehyde for 24 h at room temperature. After paraffin embedding, the tissue samples were prepared into 5 μm sections and stained with hematoxylin and eosin for 5 and 2 min, respectively. At room temperature, the tissue samples were fixed with 4% formaldehyde for 24 h. After paraffin embedding, the tissue samples were prepared into 5-μm sections, and stained with hematoxylin and eosin for 5 and 2 min, respectively. Examination under a light microscope revealed that the presence of normal kidney tissue and tumor tissue (Fig. 3A) and the tumors were composed of a single population of small, round- to oval-shaped cells with inconspicuous nucleoli, scant cytoplasm and a distinctive 'salt and pepper' chromatin pattern (Fig. 3B). The tumor cells were arranged in cords (Fig. 3C), flakes and even nest-like structures (Fig. 3D). The mitotic rate was <4/10 high-power field. The results of immunohistochemical staining indicated that these tumor cells were diffusely positive for the expression of CGA (Fig. 3E), synaptophysin (Syn) (Fig. 3F) and cluster of differentiation (CD)56 (Fig. 3G). The Ki-67 index was <10% (Fig. 3H). Therefore, a diagnosis of a right-sided renal WDNET was confirmed. At 1-year post-surgery, computed tomography indicated the absence of any residual tumor and mild hydronephrosis in the right kidney following partial nephrectomy, which indicated a good prognosis for the patient (Fig. 1C and D). Patient was followed up every 3-12 months.

Discussion

NETs are relatively rare. According to a study performed in the United States, the incidence rate is ~7 cases/100,000 individuals (3). The majority of NETs occur in the gastrointestinal tract and lung, and WDNETs account for 0.3-0.4% of all NETs (4,5). A study by McGarrah *et al* (6) indicated that the incidence of WDNETs was only 0.13 cases per 1 million subjects. WDNETs tend to occur between the ages of 40 and 70 years. No significant difference has been noted in the incidence of WDNETs between male and female patients. It has been shown that the incidence on the right side is 53.6% higher than that on the left side. The incidence in the renal parenchyma (92.8%) is significantly higher compared with that in the renal pelvis (7.2%) (7).

No neuroendocrine cells have been found in the kidney; therefore the tissue source of WDNETs is not clear, but may be related to the neural crest or pancreatic tissue that is mislocated to the kidney during embryogenesis. Multipotent stem cells differentiate into neuroendocrine cells. Chronic inflammation causes metaplasia of the pelvicalyceal urothelium. Certain

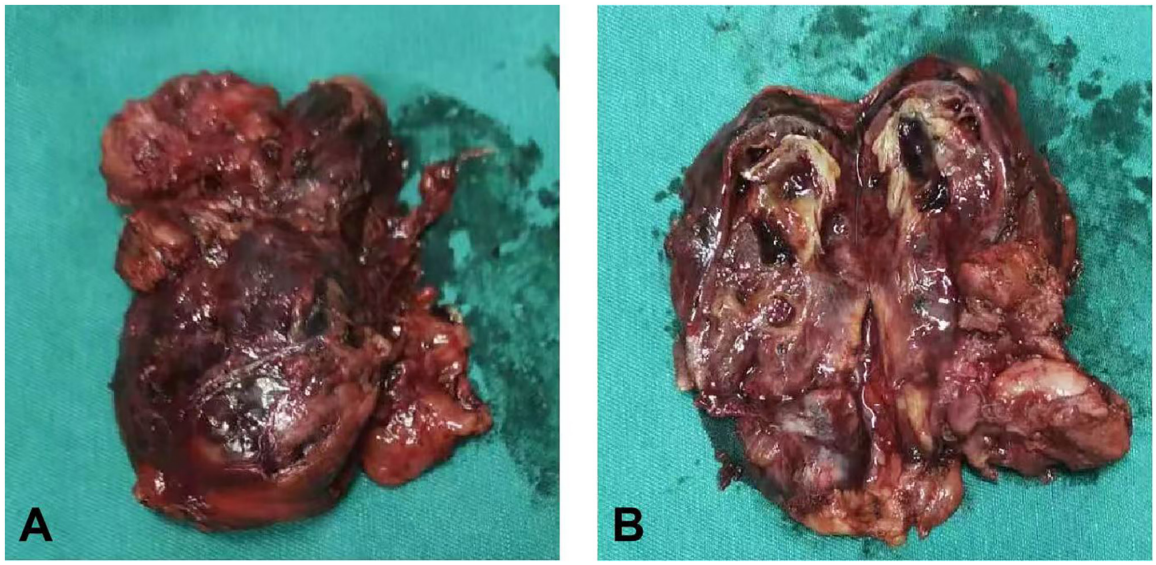

Figure 2. Gross examination of the tumor specimen. (A) A well-circumscribed, oval mass with an approximate size of 40x30x70 mm. (B) The cut surface of the tumor was gray-yellow with a complete capsule.

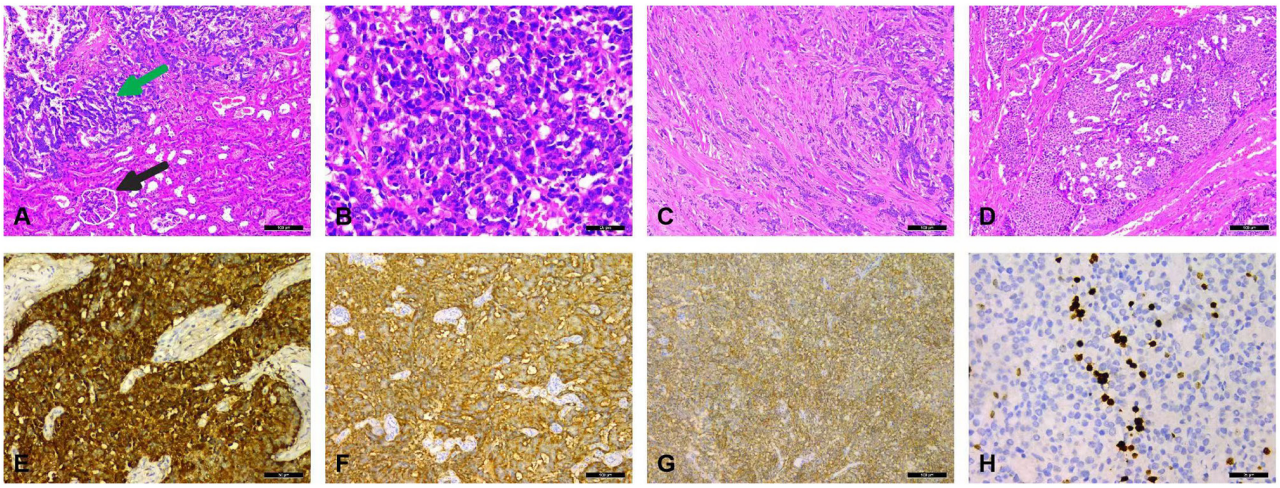

Figure 3. Pathological features of the mass. (A) The presence of normal kidney tissue and tumor tissue (the black arrow indicates the glomerulus and the green arrow indicates the tumor tissue) (H&E staining; magnification, x100). (B) The tumors were composed of a single population of small, round- to oval-shaped cells with inconspicuous nucleoli, scant cytoplasm, and a distinctive 'salt and pepper' chromatin pattern (H&E staining; x200 magnification). (C) The tumor cells were arranged in cords (H&E staining; magnification, x100). (D) Nest-like structures were present (H&E staining; magnification, x100). (E) Positive immunostaining of the tumor cells for chromogranin A expression (magnification, x100). (F) Intense positive immunostaining for synaptophysin expression in the tumor cells (magnification, x100). (G) Positive immunostaining for cluster of differentiation 56 in the tumor cells (magnification, x100). (H) The Ki-67 index was <10%. H&E, hematoxylin and eosin.

seemingly primary renal carcinoids can constitute a metastatic focus from an undiscovered primary lesion (8-11). Previous studies support a hypothesis, also known as the co-existence hypothesis, which proposes that the proliferation of scattered neuroendocrine cells originates from the epithelium of a horseshoe or polycystic kidney (12,13). It has been found that the risk of developing carcinoids in the horseshoe kidney is 62- to 82-fold higher than that noted in the normal kidney. Furthermore, in a study of renal carcinoid tumors, ~15.6% of patients had horseshoe kidneys (11).

WDNETs lack characteristic clinical manifestations, with the main reported symptoms being lumbago, abdominal swelling, an abdominal mass and hematuria. Due to the secretion of vasoactive substances by certain tumors, 10-15% of patients may have carcinoid syndromes, such as diarrhea, facial flushing and dyspnea (14,15). A total of 20-25% of patients do not present with any clinical symptoms, with the WDNET only found during routine clinical examinations (16). Conventional complementary examinations, such as CT and magnetic resonance imaging (MRI), do not distinguish WDNETs from other renal tumors. WDNETs generally present with a well-circumscribed, non-enhanced or slightly enhanced mass on CT, with a solid component; however, they are sporadically accompanied by cystic and calcified components. On MRI, WDNETs mostly demonstrate a heterogeneous signal intensity on both T1 and T2-weighted images (17). However, the signal characteristics of WDNETs are varied. The presence of

hemorrhagic necrosis in the tumor directly affects the MRI signal characteristics and is the main factor leading to signal inconsistency (17). A study has shown that gallium-68 positron emission tomography (PET)/CT is more sensitive than CT, MRI or [^{18}F]fluorodeoxyglucose-PET/CT for detecting WDNETs (18). In addition, RNA sequencing is useful for improving diagnostic accuracy; however, the patient in the present case refused to undergo this process. A diagnosis of WDNET requires pathological and immunohistochemical analyses. The majority of WDNETs are solid masses with clear boundaries and often present with grayish white or grayish brown sections (19). Hemorrhage and necrosis are rare (17). In the current study, the tumor cells were arranged into cords, ribbons and trabecular structures with abundant sinusoids. They were round or polygonal, with eosinophilic cytoplasm and unclear boundaries, round basophilic nuclei, uneven granular nuclear chromatin, mitotic appearance and rare necrosis (20). WDNETs specifically express neuroendocrine markers, such as Syn, CD56 and CGA. The specificity and sensitivity of these markers for the diagnosis of WDNETs is high. Among them, NSE exhibits high sensitivity and poor specificity, whereas CGA exhibits optimal specificity and poor sensitivity, therefore multiple markers need to be tested simultaneously for a successful clinical diagnosis (10). Previous studies have shown that insulinoma-associated protein 1 has a significant advantage with regard to the sensitivity and specificity for the diagnosis of NETs (21-23). However, prior to the diagnosis and treatment of primary renal highly differentiated endocrine tumors, metastasis to other sites should be excluded. WDNETs have a low degree of malignancy, slow growth and optimal prognosis. Surgical resection is the preferred approach for patients without metastases; however in the presence of metastasis, either pre- or post-operatively, systemic therapies for renal NETs have been directed by the treatment of non-renal NETs (24). Romero *et al* (10) indicated that ~50% of patients with WDNETs undergoing radical nephrectomy demonstrated no recurrence or metastasis following an average follow-up time of 43 months. However, it has been shown that certain cases can develop systemic multiple metastases several years after nephrectomy; therefore, patients still need to be followed up every 3 months for life even if the tumor cells are well differentiated, low grade or at an early clinical stage (25). In the present study, the postoperative pathological diagnosis demonstrated a highly differentiated NET. However, both WDNETS and renal PPGL are NETs with various similarities in their biological behavior and disease prognosis. It remains unknown whether they can be managed as a single disease. For patients from urban areas and those with a high financial status, the follow-up process should adhere to the follow-up standards for NETs, which is assessment every 3-12 months for life; however, for patients from remote rural areas and for economically disadvantaged patients, the follow-up process should adhere to the follow-up standards of non-high-risk benign PPGL, which requires only annual follow-up assessments for 10 years after surgery (26). This measure can increase the available options for patient follow-up, reduce the financial burden and psychological pressure on patients, and improve their compliance for follow-up, which in turn may be more beneficial to these patients.

In summary, WDNETs are rare, their clinical and imaging manifestations are non-specific, and the confirmation of their diagnosis depends on immunohistochemical analysis. These tumors have a low degree of malignancy and optimal prognosis, and for patients without metastases, surgical resection is the preferred approach; however, if metastases develop preoperatively or postoperatively, the systemic treatment approach for renal NETs is guided by the treatment of non-renal NETs. Certain patients can still develop recurrence and metastasis following surgery, and the postoperative follow-up needs to be performed strictly with reference to renal NETs. If patients find regular follow-up inconvenient and have financial difficulties, their follow-up can be performed according to that of non-high-risk benign PGL, which can improve patient compliance for follow-up and may be more beneficial to them.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DY and WT were the main contributors to analyzing patient data and the writing and revision of this manuscript. TW provided the initial idea and medical images. GL and ZZ provided important suggestions for the patient treatment. DY and TW confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Affiliated Hospital of Zunyi Medical University. Ethical review approval number KLL-2021-132/KLL-2021-331. Written informed consent was obtained from the patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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