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Atypical carcinoid of the primary kidney with retroperitoneal metastasis 15 years later: A case report and literature review

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ABSTRACT

Primary renal neuroendocrine tumors (NETs) are extremely rare among renal malignancies. According to pathological manifestations, carcinoid can be divided into four types: typical carcinoid, atypical carcinoid, large cell and small cell neuroendocrine carcinoma. Primary or secondary retroperitoneal carcinoid is even rarer than renal carcinoid. This article reports a patient with renal carcinoid complicated with retroperitoneal metastasis, who developed retroperitoneal metastasis 15 years after radical nephrectomy. Through the analysis of this case and the combination of the existing published literature, it is aimed to provide valuable references for clinicians in treating patients with renal carcinoid or with metastasis.

1. Background

Neuroendocrine tumors originate from neuroendocrine cells, which are distributed throughout the body. Therefore, neuroendocrine tumors can occur in any part of the body. The gastrointestinal and other digestive systems are the most common sites of occurrence, accounting for about 2/3 of all neuroendocrine tumors.[1] Neuroendocrine tumors originating from the kidney are very rare, accounting for less than 1 % of renal epithelial malignancies.[2] And there is currently no case record of renal carcinoid metastasis to the retroperitoneum. Here, we report a case of a 39-year-old female with primary renal carcinoid with retroperitoneal metastasis, who developed metastasis 15 years after radical nephrectomy. Based on the induction and analysis of the literature review, this article discusses the clinical features, differential diagnosis, imaging features, pathological manifestations, treatment options and prognosis of this case.

2. Case presentation

Initial Presentation: A 39-year-old female presented to the outpatient department due to left lumbar pain for 4 days. Physical examination showed no tenderness or percussion pain in the bilateral kidney areas, no tenderness or masses in the bilateral ureters, and no tenderness or percussion pain in the bladder area. She was admitted to the hospital after a left renal mass was detected by CT examination. There was no macroscopic hematuria, no frequency, urgency, or dysuria. There were no clinical manifestations such as fever, chills, night sweats, or fatigue since the onset of the disease. The general condition was acceptable, and no abnormalities were found on physical examination.

CT examination: A round slightly low-density mass was seen in the left renal parenchyma. The lesion locally protruded from the renal contour, with a maximum diameter of about 4.7cm × 4.3cm. The mass had a clear boundary with the renal parenchyma, and the internal density was relatively uniform. After enhancement, it showed enhancement, and the density was relatively uniform. The adjacent renal parenchyma was compressed, and the renal pelvis was slightly narrowed. It was considered a tumor, and renal cancer was more likely.

Initial Treatment and Pathology: After completing the preoperative related examinations and having no obvious surgical contraindications, left radical nephrectomy was performed under general anesthesia. After the operation, the left kidney, perirenal fat, and two renal hilar lymph nodes were sent for pathology. The pathological diagnosis was (left) papillary renal cell carcinoma of the kidney. The tumor volume was 5cm × 5cm × 4cm; the cancer tissue invaded the perirenal fat capsule; 1 out of 1 (1+/1) lymph node beside the left renal hilum showed cancer metastasis. At that time, immunohistochemistry was not done, and it was only regarded as an ordinary papillary renal cell carcinoma according to the pathology.

15 Years Later: She was admitted to the hospital due to the discovery of a left renal area mass for 1 month during a physical examination. There was no frequency, urgency, or dysuria, no macroscopic hematuria, no fever, fatigue, lumbosacral discomfort, no headache, dizziness,

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nausea, or vomiting, and the physical examination showed no abnormalities. The left renal tumer resection was performed 15 years ago. After the review, a whole abdomen (hepatobiliary pancreas spleen + retroperitoneum + pelvic cavity) CT plain scan + enhanced examination was performed due to the discovery of a mass in the left renal area: changes after left nephrectomy, and multiple nodular and mass-like soft tissue density shadows were locally seen in the left retroperitoneum, with some fusion. The larger cross-sectional size was about 40mm × 29mm × 39mm, with cystic changes inside. The local boundary with the left adrenal gland body and the left psoas major muscle was not clear. The right edge was connected with the residual left renal vein. The local abdominal aorta and lumbar artery on the left side seemed to participate in the blood supply. The plain scan CT value was about 54HU, and after enhancement, it showed mild enhancement, and there was no enhancement in the central cystic change area. The CT values in the three phases were about 70HU, 71HU, and 75HU. In addition, there were multiple soft tissue masses of different sizes at the lower edge, with no obvious cystic change area. The plain scan CT value was about 54HU, and after enhancement, it showed obvious uniform enhancement. The CT values in the three phases were 79HU, 84HU, and 75HU (as shown in Fig. 1).

Treatment and Pathology 15 Years Later: After completing the preoperative related examinations and having no obvious surgical contraindications, left laparoscopic retroperitoneal mass resection was performed under general anesthesia. The postoperative pathological section was considered recurrent or metastatic (left retroperitoneum) atypical carcinoid. There was no cancer tissue invasion in the nerves and blood vessels. Adrenal tissue was seen around, and there was no tumor involvement. Immunohistochemical results: Cancer cells Syn(+), CgA (−), CD56(+), P504S (weak+), SSTR2 (strong+), Vim(+), AE1/AE3 (weak+), CD10 (focal+), EMA (focal+), CK7(−), Pax-2(−), WT1(−), Pax-8(−), ER(−), Inhibina(−), p53 (unequal intensity +, wild type), Ki-67 (+, about 5 %)(as shown in Figs. 2–3).

Considering that the retroperitoneal atypical carcinoid may be recurrent or metastatic, immunohistochemistry was performed again on the pathological sections 15 years ago(as shown in Figs. 4–5).

We did not examine the endocrine activity of the tumor. The patient recovered well after the operation, and no other lesion locations were found in the whole body PET-CT examination.

3. Discussion

Origin and Occurrence of Carcinoid: Carcinoid mainly originates from enterochromaffin cells or gastric Kulchitsky cells and is most commonly seen in the gastrointestinal tract and can also occur in other organs. This tumor can secrete bioactive factors such as serotonin, kinins, and histamine, thereby causing blood flow dysfunction, gastrointestinal symptoms, and lesions in other parts, which is called carcinoid syndrome.[3–5] Primary carcinoid of the kidney or retroperitoneum is very rare, and metastasis from other parts of carcinoid should be excluded first. The most common metastatic site is the local lymph nodes, and

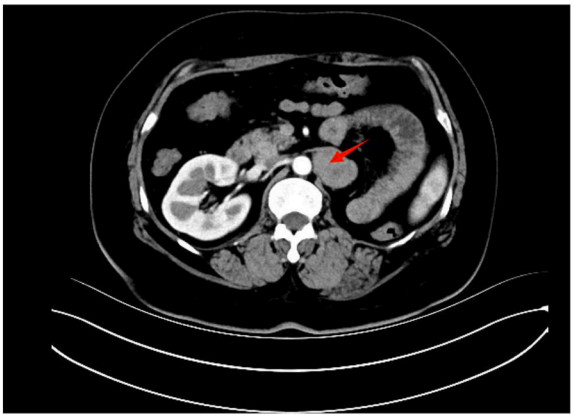

Fig. 1. Kindey CT.

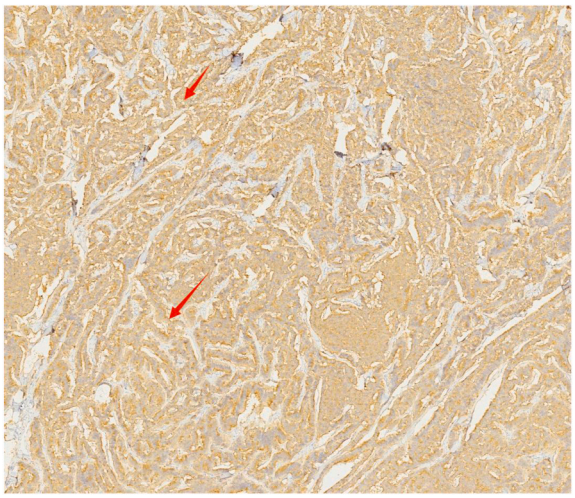

Fig. 2. Immunohistochemistry of the retroperitoneum-syn.

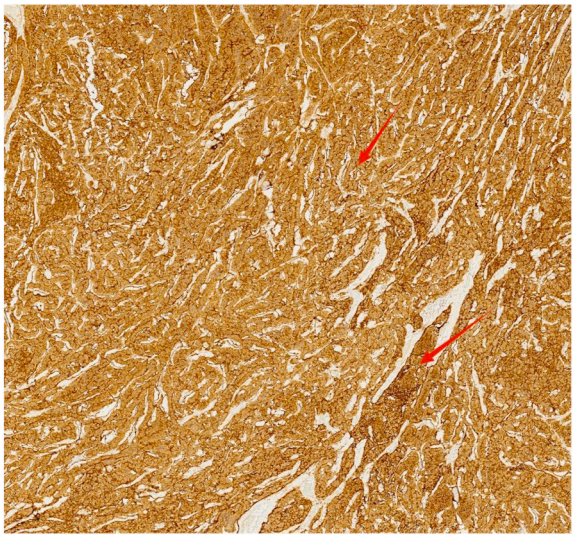

Fig. 3. Immunohistochemistry of the retroperitoneum-CD56.

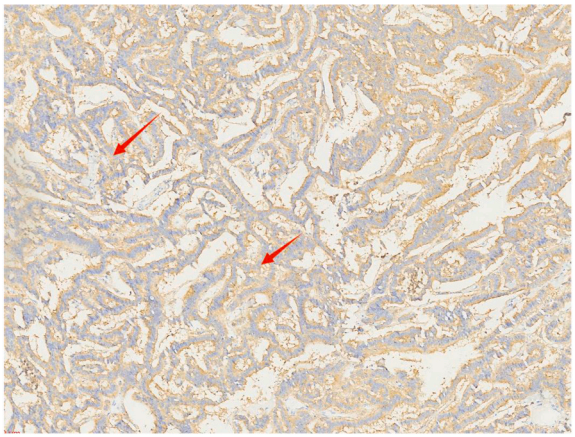

Fig. 4. Immunohistochemistry of the retroperitoneum-syn.

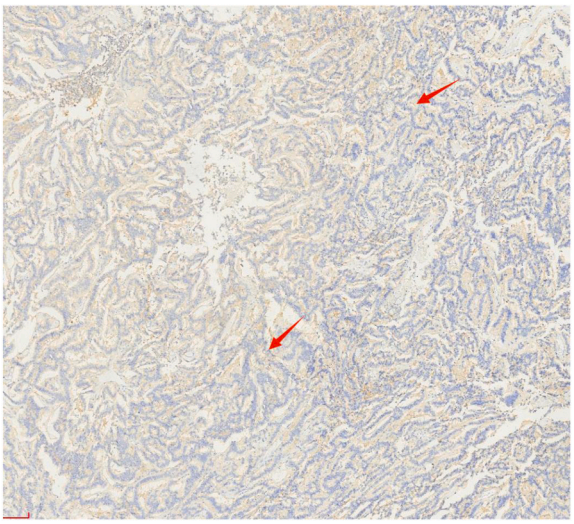

Fig. 5. Immunohistochemistry of the retroperitoneum-CD56.

other sites include the liver,[6,7] bones and lungs.

Clinical Manifestations of Renal Carcinoid: The growth process of renal carcinoid is relatively slow. About 28 % of patients are asymptomatic during physical examination.[8] Among symptomatic patients, lumbar and abdominal pain is the most common. Some patients may also have symptoms such as hematuria, constipation, and weight loss. About 25 % of patients can touch an abdominal mass.[9] Renal carcinoid is a neuroendocrine tumor that can secrete a variety of bioactive hormones into the bloodstream to produce corresponding symptoms. However, the neuroendocrine syndrome is only manifested in about 1/10 of renal carcinoid patients, and the incidence is not high. The only reported case of retroperitoneal atypical carcinoid only had the clinical manifestation of continuous severe dull pain in the lumbar and abdomen.

Differential Diagnosis of Renal Carcinoid: The differential diagnosis of renal carcinoid includes other tumors with neuroendocrine features, such as primitive neuroectodermal tumor (PNET), small cell carcinoma, neuroblastoma, paraganglioma, and metanephric adenoma. PNET can occur in a wide age range and usually presents as a monotonous cell population with bland round nuclei, and the mitotic activity can vary. Both PNET and renal carcinoid can show solid areas and rosette-like structural areas. However, different from renal carcinoid, PNET has a strong immunoreactivity to CD99. Compared with small cell carcinoma, renal carcinoid lacks an active mitotic rate, nuclear molding, apoptotic activity, necrosis, and a high proliferation index. In addition, most small cell carcinomas lack the typical tissue structure of carcinoid tumors. Both paraganglioma and neuroblastoma can mimic renal carcinoid, but they are very rare in the kidney. The neuroendocrine cells of paraganglioma are generally distributed in nests, and the granular basophilic cytoplasm is surrounded by S100 positive tentacle-like cells. Neuroblastoma shows Homer-Wright rosette-like structures and contains neurofibrillary matrix. Metanephric adenoma shows round acini with an embryonic-like appearance and often visible psammoma bodies.

Diagnosis of Retroperitoneal Carcinoid: Retroperitoneal carcinoid is very rare. When discovered, it should first be excluded whether it is transferred from other positions, such as gastrointestinal neuroendocrine tumors. When gastrointestinal tumors and peritoneal deposits show hypervascular behavior on CT or MRI and early contrast agent uptake in the arterial phase, the suspicion of neuroendocrine origin should be increased. Neuroendocrine tumors are usually small and slow-growing tumors. About 1/3 of cases may have peritoneal dissemination, and it is generally accompanied by synchronous lymph node and liver metastases.[10,11] When there is peritoneal diffusion, the most reported location of the primary tumor is the ileum or appendix.[10,12] The volume of appendiceal neuroendocrine tumors is usually very small and often difficult to identify on CT and MRI. The use of functional imaging techniques is of great help in the staging of advanced neuroendocrine tumors. Most gastrointestinal tumors can be distinguished by their unique immunochemical spectra.In gastrointestinal neuroendocrine tumors, immunohistochemical markers such as chromogranin, synaptophysin, p53, retinoblastoma protein (Rb), and Ki-67 proliferation index are also crucial for diagnosis, grading, and prognosis.[13]

Imaging Features of Neuroendocrine Tumors: The imaging features of neuroendocrine tumors lack specificity. The most common imaging feature is calcification. CT imaging of renal carcinoid usually shows a single large and well-defined renal mass. The enhanced CT shows poor or weak enhancement, corresponding to the avascular or hypovascular lesions on renal angiography. The CT manifestation of retroperitoneal carcinoid is a round soft tissue density shadow, which may have a cystic change area inside. After enhancement, it shows uneven enhancement, and the surrounding arterial tissue is suspected to participate in the blood supply. Neuroendocrine tumors usually express serum somatostatin receptors. More than 85 % of primary or metastatic carcinoids have high-affinity somatostatin receptors.[14] The radiolabeling of the somatostatin analogue octreotide is a molecular imaging method that can be used for the diagnosis and staging of carcinoid. However, in the detection of renal carcinoid, there is a disadvantage that the normal uptake of the tracer substance by the kidney may cover up the suspicious lesions of primary renal carcinoid.

Role of Immunohistochemistry in Diagnosis: Immunohistochemical staining plays an important role in the diagnosis of neuroendocrine tumors. The most common epithelial cell and neuroendogenous cell markers expressed in neuroendocrine tumors include neuron-specific enolase, synaptophysin, and chromogranin. Comprehensive literature analysis shows that most cases show strong reactivity to synaptophysin, chromogranin, CD56, Cam5.2, and vimentin, and a few cases may also show focal positivity for CK7 and CK20. TTF-1 and WT-1 negativity can exclude lung metastasis and adult Wilms tumor. Synaptophysin has high specificity for the diagnosis of neuroendocrine tumors, CD56 has high sensitivity and low specificity, and Ki-67 is helpful for observing cell activity.[15–17]

Treatment of Renal Carcinoid: The preferred treatment method for renal carcinoid is surgical treatment, and the gold standard treatment method is radical nephrectomy. According to the location, size, infiltration degree, and lymph node metastasis of the tumor, partial nephrectomy can also be selected.[18] Renal carcinoid grows relatively slowly and is a low-grade malignant tumor with a relatively good prognosis, but there is also the possibility of invasion and metastasis, and the most common is lymph node metastasis. Among NET patients with lymph node metastasis, 47 % of patients had no tumor occurrence during the average 43-month follow-up period after radical nephrectomy,[19] indicating that even if lymph nodes are metastasized, surgery can cure it.Combined use of adjuvant therapy: Somatostatin analogs can relieve related symptoms caused by excessive hormone secretion. Targeted drugs can intervene in some specific gene mutations and overexpression of proteins. External beam radiotherapy can control the growth of tumors.

Follow-up after Surgery: The follow-up after surgery is very important. The follow-up frequency depends on the patient's condition and prognostic adverse factors. Prognostic adverse factors mainly include older age, male, tumor larger than 4cm, and tumor not limited to the renal parenchyma.[20] Comprehensive literature analysis shows that there are currently no good prognostic factors to judge the prognosis of patients, but the Ki-67 index level and mitotic rate may be helpful for clinicians to predict the prognosis of similar cases.

4. Conclusion

Primary renal carcinoid is a rare malignant tumor with slow growth. The imaging diagnosis has no specific manifestations, and the diagnosis depends on pathological examination and immunohistochemical

analysis. Partial resection or radical surgical resection is a reliable method for treating renal carcinoid. Due to its possibility of recurrence and metastasis, continuous postoperative follow-up is crucial.

CRediT authorship contribution statement

Qiang Wang: Writing – review & editing, Writing – original draft. **Dong Zhuo:** Data Curation. **Houbao Huang:** Writing – review & editing. **Jianping Tao:** Writing – review & editing.

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