Differential diagnosis and unusual diffuse cytokeratin expression in renal paraganglioma: A case report

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ABSTRACT

Paraganglioma is a rare neuroendocrine tumor arising from undifferentiated cells of the primitive neural crest. We report a case of renal paraganglioma in a 67-year-old patient. Computed tomography demonstrated a solid mass in the middle and lower pole of the right kidney. Sonography revealed an enlarged right kidney with an irregular shape but distinct border. Renal cell carcinoma was diagnosed provisionally; the tumor was completely resected and submitted for pathological examination. Unexpectedly, histopathology and immunohistochemistry confirmed paraganglioma arising from the renal parenchyma. In this study, we report the exceptional occurrence of Paired box gene 8 (PAX-8) expression in a renal paraganglioma. In addition, we demonstrated diffuse cytokeratin positivity in this renal paraganglioma. Although our report of a paraganglioma originating from the kidney is not unique, our finding expands the known immunophenotypic spectrum of this tumor. The awareness of the possible occurrence of cytokeratin diffuse positivity in paraganglioma is relevant to avoiding misdiagnosis of paraganglioma.

KEY WORDS: Cytokeratin, differential diagnosis, diffuse expression, kidney, paraganglioma

INTRODUCTION

Paragangliomas are rare tumors arising from extra-adrenal chromaffin tissue, which is the paraganglia. They are widely distributed near or within the autonomic nervous system in a variety of retroperitoneal sites and in the sympathetic ganglia of various viscera. All paragangliomas are believed to originate from the neural crest. Rare sites for paragangliomas include the uterus, prostate, bladder, urethra, kidney, carotid body, larynx, nasal cavity, paranasal sinuses, thyroid gland.[1‑5] Renal paragangliomas are both rarely encountered and difficult to distinguish clinically and pathologically. Herein, a case of renal paraganglioma in a 67-year-old man is described. The relevant differential diagnoses are discussed.

CASE REPORT

A 67-year-old male patient, with an unremarkable medical history, presented with an asymptomatic kidney mass that was discovered incidentally. Computed tomography demonstrated a solid mass in the middle and lower pole of the right kidney [Figure 1]. Sonography revealed an enlarged right kidney with an irregular shape but distinct border. Renal cell carcinoma was the provisional diagnosis, and surgical exploration was performed. The tumor was located in the middle and lower pole of the right kidney, was 5 × 5 cm in size, was maroon in color, had a complete capsule and did not invade neighboring tissues [Figure 2a]. Neither tumescent lymph nodes surrounding the kidney nor vessel tumor embolus were detected. Involvement of the right renal pelvis and ureter was not found. After inspection, the tumor was completely resected and submitted for pathological examination. Microscopically, the tumor consisted of spindle cells and epithelioid cells encapsulating central fibrovascular tissue [Figure 2b and c]. Immunohistochemistry revealed that the tumor was positive for CD56 [Figure 2d], synuclein (Syn) [Figure 2e], chromogranin a (CgA) [Figure 2f], neuron-specific enolase (NSE), vimentin, Paired box gene 8 (PAX-8) [Figure 2g], and was focally positive for inhibin and vascular endothelial growth factor (VEGF).

How to cite this article: Wang J, Zhong L. Differential diagnosis and unusual diffuse cytokeratin expression in renal paraganglioma: A case report. Indian J Pathol Microbiol 2020;63(Special):S41-3
The Ki-67 proliferation index was less than 2%. Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) and CD34 highlighted the vascular supporting network. Notably, diffuse expression of cytokeratin was found [Figure 2h]. The tumor was negative for epithelial membrane antigen (EMA), renal cell carcinoma (RCC) [Figure 2i], S-100, smooth muscle actin (SMA), melanoma antigen recognized by T cell-1, (MARE-1/Melan-A) [Figure 2j], HMB45 [Figure 2k] and CD10. Moreover, the tumor was devoid of S-100 protein positive cells [Figure 2l]. Based on these findings, paraganglioma arising from the renal parenchyma was diagnosed histologically.

**DISCUSSION**

Paraganglioma arising from the kidney is rare. Its pathogenesis is unknown. Zhao et al.\(^6\) postulate that the ectopic adrenal tissue or adrenal rests in kidney could be a plausible origin of the lesion. Another possibility is that paraganglioma may originate from entrapped neuroendocrine progenitor cells of the dispersed neuroendocrine system resulting from aberrant migration from the neural crest during embryogenesis.

We describe a patient with renal paraganglioma. Paraganglioma is a neuroendocrine tumor, and microscopically, the tumor consisted of spindle cells and epithelioid cells encapsulating central fibrovascular. Therefore, the differential diagnosis considered included carcinoid, metastatic paraganglioma, hemangioblastoma, epithelioid angiomylipoma and RCC. Paragangliomas have a characteristic nesting growth pattern; the tumor consisted of a defined nest of spindle-shaped and oval-shaped cells (“Zellballen”), whereas the nests of carcinoid tumors have a typical endocrine appearance with small round cells having small round nuclei. In this case, immunohistochemical profile may not help to distinguish paraganglioma from carcinoid. However, the morphologic features favored paraganglioma rather than carcinoid. Because benign and malignant paragangliomas have the same histological appearance, and benign appearing tumors can metastasize to lymph nodes and other distant, non-parangliia affiliated anatomic sites, the possibility of a metastatic paraganglioma must be considered in the differential

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**Figure 1:** Computed tomography (CT) revealed a solid tumor with clear border in the right kidney

**Figure 2:** The resected tumor (a) and histological examination with HE (hematoxylin and eosin) staining (b and c) (Low magnification and high magnification) and immunohistochemistry (d-l). HE staining displayed a defined nest consisting of cells surrounding fibrovascular substances. Immunohistochemistry showed tumor cells are positive for CD56 (d), Syn (e), CgA (f), and PAX-8 (g). Diffuse positivity for CK (h). The tumor cells were negatively stained for RCC (i), Melan-A (j), and HMB45 (k). Sustentacular cells and tumor cells were negative for S-100 (l)
RCCs are composed of polygonal or cuboidal cells with clear or granular-eosinophilic cytoplasm. The pattern of growth can be predominantly solid, alveolar and acinar, separated by fibrovascular septa, but may be admixed with cystic, papillary, tubular, and sarcomatoid patterns. The similar morphologic and immunophenotypic features hinders distinguishing these two entities. RCCs are frequently immunoreactive with antibodies to cytokeratin, EMA, vimentin, RCC and CD10; this reactivity is not seen in paragangliomas. In this case, the tumor cells were EMA, RCC and CD10 negative combined with positivity for cytokeratin, vimentin, CD56, Syn, CgA and NSE. Moreover, paraganglioma lacks the morphologic diversity that is seen in RCCs.

The loss of S-100 protein has been reported to correlate with a more biologically aggressive clinical course for pheochromocytomas and paragangliomas. In a study reported by Granger et al., metastatic paragangliomas contained sustentacular cells in both the primary and metastatic lesions. The presence of sustentacular cells in the primary tumors could not be used as an absolute indicator of tumor metastatic potential. In this case, the sustentacular cells were absent. It should be noted that absence of sustentacular cells is not required for a diagnosis of malignancy. Distant metastases and invasion of adjacent organs are the only reliable indicators of malignancy. There are no definite microscopic criteria to distinguish between benign from malignant tumors. A proliferation index for Ki-67 may contribute to the differential diagnosis. Due to the different scoring protocols using cell counts, use of the Ki-67 proliferation index to assess malignancy is not widely accepted in clinical practice.

Positive immunoreactivity to PAX-8, which was not reported previously in renal paraganglioma, was unexpected and contrasts with adrenal pheochromocytoma and paraganglioma in the other organs of the human body that are essentially always negative for PAX-8. In this study, we report the exceptional occurrence of PAX-8 expression in a renal paraganglioma. This novel finding adds support to the hypothesis that the immunoprofile of extra-adrenal pheochromocytoma varies with site of origin, perhaps as a result of tumor cell lineage and retention of organ-specific markers, or acquisition of site-specific antigens due to local factors.

Although our report of a paraganglioma originating from the kidney is not unique, our finding expands the known immunophenotypic spectrum of this tumor. Notably, to the best of our knowledge, to date, all reports of paragangliomas immunohistochemically tested for cytokeratin expression were negative with the exception of reports of focal positivity in a very small number of cases. However, the awareness of the possible occurrence of cytokeratin diffuse positivity in paraganglioma is relevant to avoiding misdiagnosis of paraganglioma.

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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