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CASE REPORT

Combined renal clear cell and papillary carcinoma with neuroendocrine dedifferentiation: a very rare entity

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ABSTRACT

Background: There are only few documented cases of neuroendocrine differentiation in clear cell renal cell carcinoma .

Methods: This is a case report of a combined renal clear cell and papillary carcinoma with neuroendocrine differentiation arising in an 81-year-old male.

Results: Immunohistochemistry revealed positivity for PAX8, AMACR and CD10. RCC, synaptophysin, chromogranin, WT-1, CK20, CK7, HMW CK, desmin, CD117 and PAX-2 were all negative. Immunoreactivity for NSE, CD56 and vimentin in the spindle cell component was noted. Ki-67 reactivity was variable.

Conclusion: It is suggested that immunohistochemistry for neuroendocrine differentiation should be performed in any high grade component of renal cell carcinoma (RCC) to facilitate their identification.

Introduction

Renal neuroendocrine tumors are extremely rare. By definition, a primary renal neuroendocrine tumor occurs within the renal parenchyma with histological and immunohistochemical features of neuroendocrine differentiation. These are classified as well differentiated tumors including renal carcinoid tumours and atypical carcinoid tumors and high grade tumors which include large cell and small cell neuroendocrine carcinoma.[1] Though neuroendocrine differentiation is a well-recognized entity in tumors like gastrointestinal adenocarcinoma, small and large cell carcinoma of the lung, prostatic adenocarcinoma, urothelial carcinoma, ovarian carcinoma and certain breast carcinomas.[2] There are very few documented cases of neuroendocrine differentiation in Renal Cell Carcinomas. It has only been described recently in chromophobe renal cell carcinoma. We present a case of an elderly male patient with a 95mm mass in left kidney revealing a combined clear cell and papillary RCC with neuroendocrine differentiation.

Case Report

An 81-year-old male patient; otherwise, asymptomatic, presented to the hospital with unintentional weight loss of around 6-7 kilograms over the last few months.

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His history was unremarkable for hematuria, abdominal pain or related urinary manifestations.

All laboratory tests including prostate specific antigen (PSA) and creatinine were within normal limits. Left radical nephrectomy was performed.

Pathological Findings:

Gross Features:

The resected specimen consisted of a left kidney measuring 120x70x65mm. Serial slicing revealed a grey, white lobulated mass measuring 95x60x40mm with focal areas of hemorrhage and necrosis (Figure 1). The lesion grossly involved the renal sinus fat and hilar vascular margin. However, it was located 2mm away from the nearest inked capsular surface. Adrenal gland was not identified.

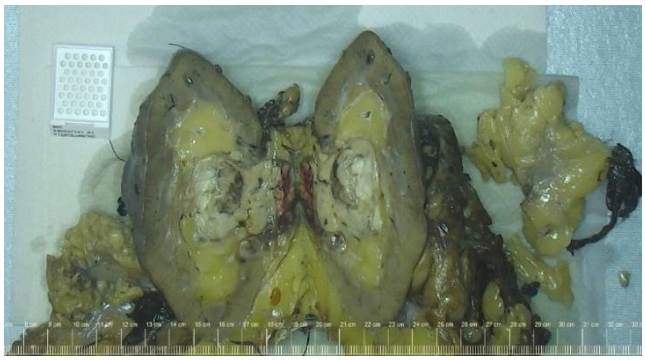

Figure 1: gross image of left kidney revealing a grey, white mass involving the renal sinus fat.

Microscopic Features:

Sections from the lesion revealed a renal cell neoplasm predominantly composed of sheets of clear cells with foci of trabecular growth and oncocytic change admixed with a papillary architecture. In addition, a focal spindle cell component with nuclear palisading and pseudo-rosette formation was also identified (Figure 2). Nucleoli were prominent at 10x objective (Furhman grade 3). Multiple foci of lymphovascular invasion were identified. The neoplasm infiltrated the renal sinus fat and renal vascular margin.

An expert opinion was sought and a final diagnosis of a combined clear cell and papillary RCC (CCPRCC) with neuroendocrine differentiation was made.

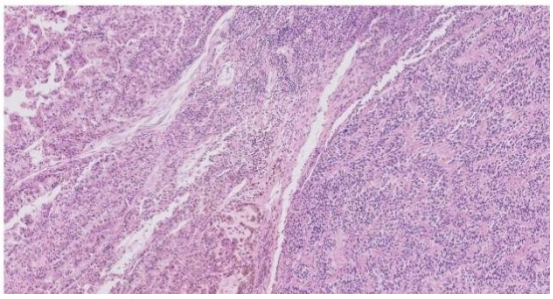

Figure 2: microscopic section showing the sharp interphase between the clear cell renal and papillary carcinoma and the spindle cell component revealing the pseudorosetting (H&E x10).

Immunohistochemistry:

Immunohistochemistry revealed positivity for PAX8, AMACR and CD10 supporting the clear cell and papillary RCC pattern. A strong positivity for NSE, CD56 and Vimentin in the spindle cell component was also noted. Ki-67 was variable. However, RCC, synaptophysin, chromogranin, WT-1, CK20, CK7, HMW CK, desmin, CD117 and PAX-2 were all negative (Figure 3).

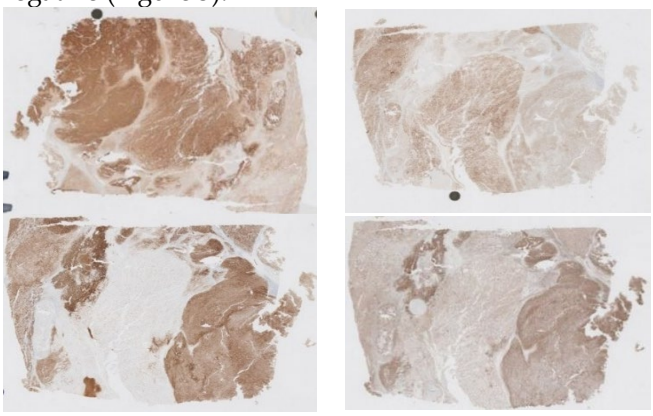

Figure 3: Immunohistochemical staining of the spindle cell component showing positive staining for AMACR (top left), CD10 (top right), NSE (bottom left) and vimentin (bottom right).

Discussion

Renal cell carcinoma comprises of a broad spectrum of histopathological entities classified on the basis of their diverse morphological patterns, molecular pathogenesis including cytogenetic and genetic analysis, aetiology and clinical behaviour.[3] These represent 2-3% of all neoplasms with a peak incidence between 60 to 70 years and a male predominance with a 1.5:1 ratio. The definitive risk factors include smoking, hypertension and obesity amongst others.[4]

Renal cell carcinomas were described in the 2004 World Health Organization (WHO) classification which has evolved and modified over the years by the International Society of Urological Pathology (ISUP) Vancouver in 2012 and finally the contemporary WHO 2016 classification. In addition to the three main RCC types: clear cell (ccRCC), papillary (pRCC -type I and II) and chromophobe (chRCC) the number of recognized subtypes has increased in this process.[5] The critical steps in the diagnostic approach includes recognizing the underlying morphologic pattern, assessing the predominant cell type and search for additional or minor component supported by immunohistochemistry.[5]

Neuroendocrine tumors can arise in any tissue or organ from the differentiation of primitive totipotent stem cells. These can occur in pure form or mixed with other non-endocrine tumors. However, the kidney is an unusual site for such combined tumors.[6] The association of a neuroendocrine component with clear cell renal carcinoma is very rare and only a few case reports have been documented.[5] Primary renal neuroendocrine neoplasms including carcinoid, small cell carcinoma and large cell neuroendocrine carcinoma are extremely rare entities with diverse morphology and biological behaviour.[6]

The morphologic features suggestive of neuroendocrine differentiation consist of organoid growth patterns characterized by trabecular, insular, palisading, ribbon and rosette-like structures. The tumor cells are uniform and polygonal with finely eosinophilic cytoplasm, round to oval nuclei with a "salt and pepper" chromatin pattern. Necrosis is usually absent. Stroma is highly vascular with hyalinization sometimes with cartilage or bone formation as well as amyloid deposition.[2]

Immunohistochemistry plays a critical role in the diagnosis. In the present case, there were no clinical manifestations or radiologic evidence to support a pre-operative diagnosis of a neuroendocrine component. Pan RCC markers PAX-8 and CD10 were extensively

positive in all the three components supporting the renal origin. AMACR was positive in the papillary component. There was a lack of staining for CK7 and CK 20. The spindle cell component was negative for synaptophysin and chromogranin. However, a strong positivity for NSE, CD56 and Vimentin was noted.
The treatment for typical clear cell carcinoma includes anti angiogenic therapy in addition to surgery. The neuro endocrine component poses aggressive behavior. However, optimal treatment for a renal cell carcinoma with neuroendocrine differentiation is unknown at present due to the rarity of cases.[7]

Conclusion

The present case re-emphasizes the complexity and heterogeneity in renal cell carcinomas. It is suggested that immunohistochemistry for neuroendocrine differentiation should be performed in any high grade component of RCC to facilitate their identification.

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