

## Case Report

# Concurrent primary carcinoid tumor arising within mature teratoma and clear cell renal cell carcinoma in the horseshoe kidney: report of a rare case and review of the literature

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**Abstract:** Primary carcinoid tumor arising in a mature teratoma of the horseshoe kidney is exceptionally rare and only 4 such cases have been reported in the world literature to date. The simultaneous occurrence of different subtypes of renal cell carcinoma (RCC) or RCC coexistence with non-RCC neoplasms from the same kidney is unusual and infrequently reported. Herein we report a case of primary carcinoid tumor arising within mature teratoma, concurrent with a clear cell RCC in the horseshoe kidney of a 37-year-old man. Histologically, both the carcinoid tumor and clear cell RCC demonstrated the characteristic morphology in their classic forms. In addition to the carcinoid tumor, the mature teratoma consisted of variably sized, large cystic spaces lined by cytologically bland mucinous columnar epithelium, pseudostratified columnar epithelium, ciliated epithelium and mature smooth muscle fibers were also identified within the cystic wall. Furthermore, foci of round, small nodules composed of mature prostatic acinus were noted in the teratoma which was confirmed by exhibiting strong immunoreactivity for prostate specific antigen. The present case serves to expand the histologic component that may be encountered in the mature teratoma of the kidney and further broadens the spectrum of primary tumors occurring in the horseshoe kidney.

**Keywords:** Kidney, carcinoid tumor, mature teratoma, horseshoe kidney, prostate tissue

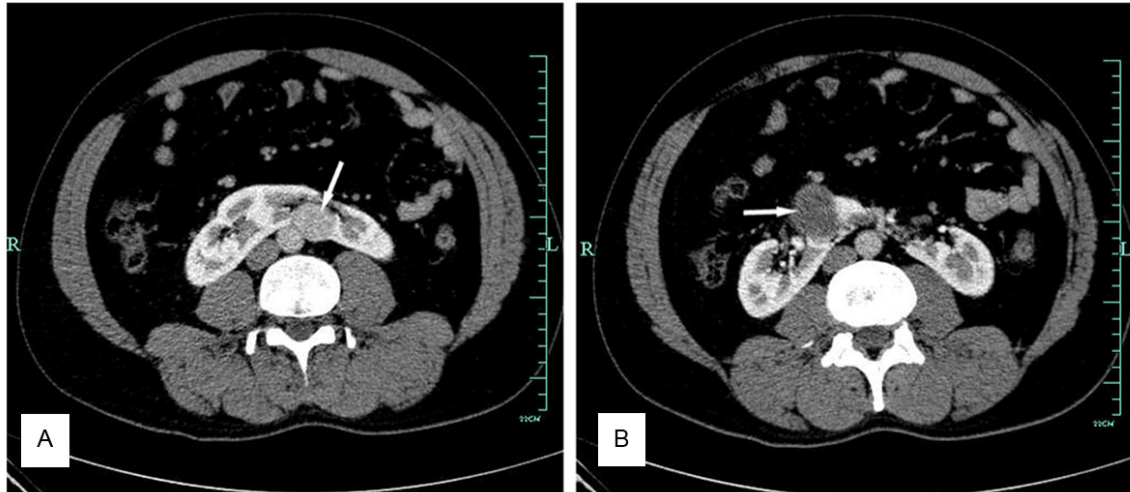
## Introduction

The neuroendocrine tumor (NET) is a rare neoplasm share a phenotype notable for neuroendocrine and neural differentiation. The classification of NET largely depends upon the anatomical site and organ of origin. According to the World Health Organization (WHO) classification of lung NET [1], the renal NET is currently classified into four categories: typical carcinoid, atypical carcinoid tumor, small cell carcinoma, and large cell neuroendocrine carcinoma. Primary carcinoid tumor of the kidney is very rare because neuroendocrine cells are not found within normal renal parenchyma [2]. Since then, not more than 100 cases have been reported in the literature [3], and approximately 30 cases were associated with horseshoe kidneys, while 4 cases were found in a mature teratoma [4-7]. Because of the rarity of this entity, we present a new case of concurrent

primary carcinoid tumor arising in a mature teratoma and clear cell RCC in the same horseshoe kidney. Additionally, the present case revealed prostatic glands in teratoma, and to the best of our knowledge, prostatic differentiation as part of mature teratoma of the kidney has never been previously reported.

## Case presentation

A 37-year-old man was referred to our hospital for further evaluation of an incidentally found renal mass on computed tomography (CT) in a local clinic. The clinical was negative and all laboratory data were within the normal limits. He had no symptoms of carcinoid syndrome. There was no family history of renal failure or other familial syndrome. He had a medical history of the right thyroid lobectomy plus group VI lymph nodes dissection for ipsilateral papillary thyroid carcinoma. Contrast-enhanced CT scan



**Figure 1.** Computed tomography scan of abdomen and pelvis demonstrates horseshoe shaped kidney. A: A mass in the lower pole of the left kidney and in isthmus (arrow). B: A cystic tumor in the lower pole of the right kidney and in isthmus (arrow).

of the abdomen and pelvis revealed horseshoe shaped kidney and a well-defined and encapsulated solid mass (2.4×2.4 cm) at the lower pole of the left kidney and in isthmus (**Figure 1A**). In addition, within the lower pole of the right kidney, also in isthmus, a cystic mass (5.2×5.2 cm) was identified (**Figure 1B**). No extension into the inferior vena cava and renal veins was detected. No other lesions were recognized in the gastrointestinal tract or elsewhere in the body. The bilateral renal tumors in isthmus of the horseshoe kidney were surgically resected with 1 cm excellent margin of normal parenchyma. No other lesions were present in the adjacent renal parenchyma. He received no adjuvant therapy. The postoperative period was uneventful. The patient remains in complete remission after 9 months of follow up.

## Methods

The resection specimen has been fixed in 10% buffered formalin and routinely processed to paraffin wax. Serial sections were stained with hematoxylin and eosin. Immunohistochemistry was performed on 3mm sections cut from paraffin blocks using avidin-biotin-complex immunoperoxidase technique and the following antibodies: pancytokeratin, synaptophysin, chromogranin A, CD56, CD99, desmin, Wilms tumor protein (WT1), PAX-8, thyroid transcription factor-1 (TTF-1), Ki-67 and prostate-specific antigen (PSA).

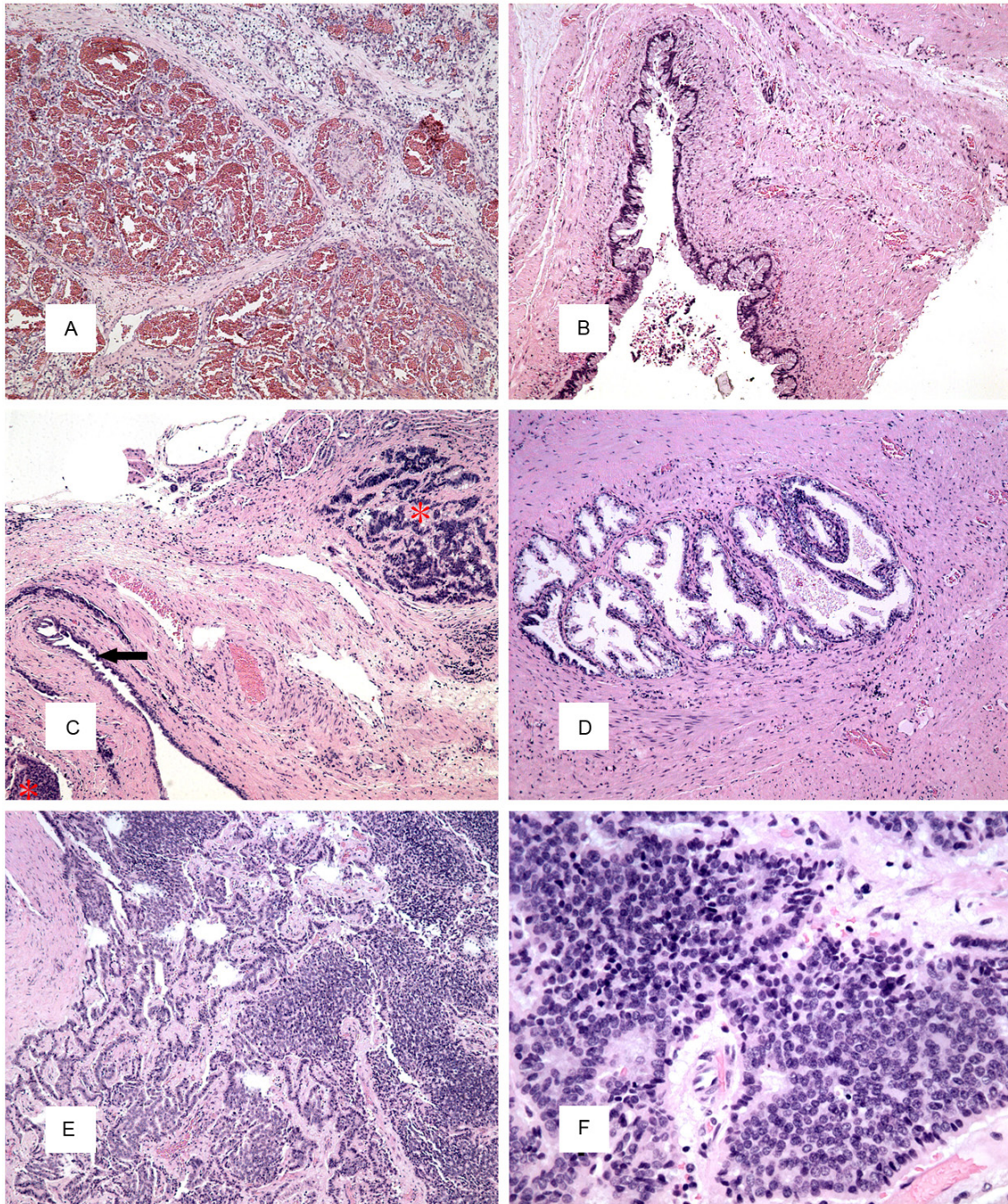
## Pathologic findings

Grossly, the left renal tumor, measuring 2 cm in maximum diameter, had a solid and hemorrhagic cut surface and well circumscribed. The right cystic mass measuring 5×5×5 cm was surrounded by a capsule and the cyst was filled with friable blood clot.

Microscopically, the smaller, left tumor was composed of strikingly clear cells arranged predominantly in an alveolar pattern and the cystic dilatation of the larger alveoli was filled with fresh blood (**Figure 2A**). Some clear cells were organized in acinar and tubule structures. All patterns had a characteristic prominence of microvasculature network embedded in the tumor cells. The grade of the tumor was grade 2 using Fuhrman nuclear grading system. The diagnosis was made to be conventional type, clear cell RCC, Fuhrman nuclear grade 2.

Microscopic examination the larger, right cyst mass revealed two components. The first component was multilocular cystic spaces lined by mucinous columnar or colonic-like epithelium (**Figure 2B**), pseudostratified columnar epithelium and ciliated epithelium (**Figure 2C**), and containing smooth muscle, mature adipose and nerve bundles in the wall. Focal of the cystic spaces was not lined by any epithelium, which had been destroyed by the hemorrhages, but being lined by several layers of hemosiderin-laden macrophages. There were focal glands



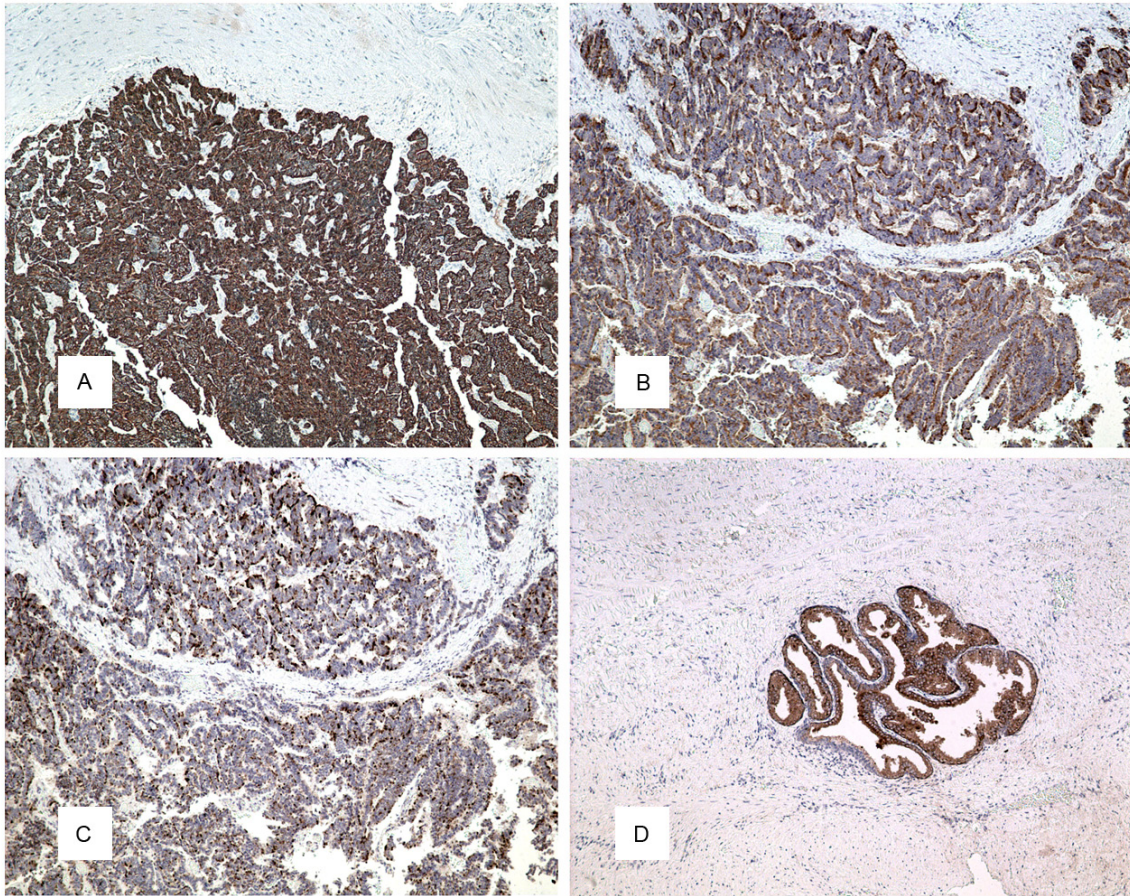


**Figure 2.** Histopathologic features: A: Clear cell carcinoma. Cystic dilatation of the larger alveoli or tubules were filled with fresh blood. B: Teratomatous components of mucinous columnar epithelium. C: Teratomatous components of ciliated epithelium (arrow) and carcinoid tumor (asterisk) underneath and closely apposed to the epithelial lining of the teratomatous cysts. D: Prostatic glands surrounded by smooth muscle. E: Carcinoid tumor showing the trabecular and solid of monotonous and round cells. F: Nuclei were round and the nuclear chromatin showed "salt-and-pepper" pattern. (A-E:  $\times 100$ , F:  $\times 400$ ).

morphologically compatible with prostatic differentiation with a lobular arrangement of medium-sized acini lined by cuboidal to columnar cells with small round nuclei and inconspic-

uous nucleoli. The cytoplasm was pale to clear. The basal cells were small and located at the periphery of the glands (**Figure 2D**). All these findings in the first component represented a





**Figure 3.** Immunohistochemical findings. Pancytokeratin (A), synaptophysin (B) and chromogranin A (C) all staining were positive in the carcinoid tumor. D: The prostatic glands showed positivity for PSA. (A-D:  $\times 100$ ).

mature cystic teratoma. The second component of the tumor showed trabecular and anastomosing ribbon-like growth pattern admixed with solid nests (**Figure 2E**), with prominent fibrovascular septa along with focal prominent lymphocytic infiltrate. Foci of rosette-like arrangements were present. The tumor were composed of monotonous, small cells with scant and narrow rim of eosinophilic cytoplasm, round to oval nuclei with fine granular “salt-and-pepper” chromatin, and absent to inconspicuous nucleoli (**Figure 2F**). Small focal calcifications were present in the cystic wall. However, neither necrosis nor mitotic activity was appreciated. These features of the second component represented a carcinoid tumor. The carcinoid tumor components were found underneath and closely apposed to the epithelial lining of the teratomatous cysts (**Figure 2C**). The non-neoplastic kidney demonstrated mild chronic interstitial inflammation. Basing on these findings, the diagnosis was made to be primary car-

cinoid tumor arising within mature teratoma. All surgical resection margins were negative.

Immunohistochemically, the carcinoid tumor component was positive for pancytokeratin (**Figure 3A**), synaptophysin (**Figure 3B**), chromogranin A (**Figure 3C**), CD56 and CD99, while stains for desmin, WT1, PAX-8 and TTF-1 were negative. A very low proliferation rate ( $<3\%$ ) was seen by Ki-67 staining. The prostatic-type glands showed diffuse positive for prostate-specific antigen (**Figure 3D**).

#### Discussion

Primary carcinoid tumor of the kidney is rare. Since the first report by Resnick et al in 1966 [8], less than 100 cases have been documented in the literature to date [3]. These arise equally frequently in men and women, and the patients' ages have ranged from adolescence to the seventh decade of life with a mean age of approximately 50 years. Clinical presentation is

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**Table 1.** Clinical characteristics of primary carcinoid tumor arising with mature teratoma of the horseshoe kidney

Author, year	Sex/age	Clinical presentation	Metastasis de novo	Treatment	Follow-up
Fetissov et al, 1984	Male/65	Fever	No	Radical nephrectomy	Not available
Lodding et al, 1997	Male/23	Abdominal pain	No	Radical nephrectomy	ANED at 120 months
McVey et al, 2002	Male/39	Pruritus, weight loss	Yes (liver)	Partial nephrectomy, alcohol injection liver metastasis	AWD, liver and lumbar spine metastasis at 72 months
Armah et al, 2009	Female/50	Low back and right hip pain	No	Partial nephrectomy	ANED at 6 months
Current case	Male/37	Asymptomatic	No	Partial nephrectomy	ANED at 9 months

ANED=alive with no evidence of disease, AWD=alive with disease.

**Table 2.** Pathologic characteristics of primary carcinoid tumor arising with mature teratoma of the horseshoe kidney

Author, year	Side/Size cm	Components of mature teratoma	Cytologic features of NET	Mitotic rate/necrosis	Coexisted tumor
Fetissov et al, 1984	Right/2	Transitional and mucinous columnar epithelium with occasional cilia, smooth muscle, ossified chondroid plaques, nerve bundles with ganglion cells	NP	NP/NP	No
Lodding et al, 1997	Right/2	Mature bone	Uniform cells	NP/NP	No
McVey et al, 2002	Right/9.5	Ossification	Round and oval cells containing hyperchromatic nuclei and moderately abundant granular cytoplasm, focal nuclear enlargement and pleomorphism	5-6/10HPF/Yes	No
Armah et al, 2009	Right/9.7	Mucinous columnar enteric-type or colonic like epithelium and ciliated epithelium, smooth muscle	Small round cells with fine granular "salt-and-pepper" chromatin pattern, and peripheral palisadind.	0/10HPF/No	Primary invasive moderately differentiated adenocarcinoma arising within mature teratoma
Current case	Right/5	Mucinous columnar enteric-type and ciliated epithelium, smooth muscle, prostatic tissue, mature adipose, nerve bundles	Monotonous small round cells with "salt-and-pepper" and inconspicuous nucleoli	0/10HPF/No	Clear cell RCC

NP=not provided, HPF=high power field, RCC=renal cell carcinoma.

not different from that of any other renal neoplasm, with abdominal, back or flank pain, followed by abdominal mass and hematuria. About 28.6% of patients were asymptomatic at the time of discovery. Only 12.7% of patients have been associated with the carcinoid syndrome. In general, metastases were present in 45.6% of patients at initial diagnosis [9], with regional lymph nodes and liver being the most frequently affected organs, followed by bone and lung. Importantly, despite widely metastatic disease, patients tend to have a prolonged clinical course.

Primary carcinoid tumor is often associated with horseshoe kidney, renal teratoma and

polycystic kidney disease [3]. To date, approximately 30 cases of primary carcinoid tumors within a horseshoe kidney were found in the literature. But only 9 cases of primary carcinoid tumors arising within mature teratoma of the kidney have been found in the world [4-7, 10]. We identified a total of 4 cases of primary carcinoid tumors arising within mature teratomas of the horseshoe kidney in the medical literature [4-7]. All 5 patients (including our current unpublished case) demographics and clinical features were summarized in **Table 1**. There was a striking male predilection (M:F=4:1). Patients' mean age was 43 years (range: 23-65). The clinical presentation of the 5 cases was variable, but none was associated with



carcinoid syndrome. Clinical followed up data were obtained for 4 patients, ranging from 6 to 120 months (mean: 52 months). Pathologic characteristics of the 5 cases were summarized in **Table 2**. All of the 5 cases involved the right kidney of the horseshoe kidney. The tumor size ranged from 2 to 9.5 cm (mean: 5.6 cm). The mitotic rate of the tumor was quantified in 3 of the 5 cases as 0/10HPF in 2 cases, the other one case that demonstrated the highest mitotic rate (5-6/10HPF) belonged to the patient who was still alive 6 years after partial nephrectomy and alcoholization of liver metastases and 3 year after the appearance of bone metastases. This tumor also exhibited focal necrosis. As defined in the lung, only this patient was diagnosed with atypical carcinoid [6].

The current case has two unusual pathologic characteristics: one is focal prostatic component in the mature teratoma; the other is coexistence carcinoid tumor, mature teratoma and clear cell RCC in the horseshoe kidney. Prostate tissue has rarely been described in ovarian and testicular teratomas, but never has been found in the mature teratoma of the kidney [11, 12]. Our case seems to be the first report describing prostatic glands in a mature teratoma of the kidney. RCC is the type of tumor most frequently associated with horseshoe kidney, but the concurrent carcinoid tumor and clear cell RCC in the horseshoe kidney has never been reported previously.

The histogenesis of renal carcinoid tumor is uncertain since no neuroendocrine cells have been identified in the normal kidney [2]. Theories regarding their putative origin from multipotential stem cells, entrapped neural crest cells in the metanephros during embryogenesis and hyperplasia of preexisting neuroendocrine cells within metaplastic of teratomatous epithelium [3]. Jeung et al recent published a study on 9 cases of primary renal carcinoid tumor, which showed all the 9 cases were absence of the expression of PAX-2 and PAX-8, which are thought to be associated with the developing mesonephric tissue. It may support the theory that these are derived from extrarenal elements [13].

The differential diagnosis of renal carcinoid tumor includes small cell carcinoma, primitive neuroectodermal tumor (PNET), and metanephric

adenoma. Small cell carcinoma exhibits high grade cellular atypia and high mitotic/proliferative indices. Tumor necrosis is often extensive [14]. Renal PNETs are rare and they have more of a monotonous proliferation of small rounds in sheets, associated with which is a prominent ramifying capillary network. Variable mitotic figures and pseudorosettes can be seen. They are characteristically positive for CD99 and EWS-FLI1 fusion transcription, and are usually negative for pancytokeratin, synaptophysin and chromogranin, unlike renal carcinoid tumors [15]. Metanephric adenoma shows very small cells with very little cytoplasm forming very small tubules in an acellular stroma. In contrast to renal carcinoid tumors, metanephric adenomas lack well-developed neuroendocrine features with lack of immunoreactivity for neuroendocrine markers but positive for WT1 [16].

In conclusion, neoplasms originating within the horseshoe kidney are rare. We describe a unique case of concurrent clear cell RCC and primary carcinoid tumor arising within mature teratoma in the horseshoe kidney. Furthermore, our case revealed mature prostate gland tissue in teratoma, which, to our knowledge, represents the first example of this rare phenomenon to occur in the mature teratoma of the kidney.

### Disclosure of conflict of interest

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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### References

- [1] Beasley MB, Brambilla E, Travis WD. The 2004 World health Organization classification of lung tumors. *Semin Roentgenol* 2005; 40: 90-97.
- [2] Guy L, Bégin LR, Oligny LL, Brock GB, Chevalier S, Aprikian AG. Searching for an intrinsic neuroendocrine cell in the kidney. An immunohistochemical study of the fetal, infantile and adult kidney. *Pathol Res Pract* 1999; 195: 25-30.

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- [3] Kuroda N, Tanaka A, Ohe C, Mikami S, Nagashima Y, Inoue K, Shuin T, Taguchi T, Tominaga A, Alvarado-Cabrero I, Petersson F, Brunelli M, Martignoni G, Michal M, Hes O. Review of renal carcinoid tumor with focus on clinical and pathobiological aspects. *Histol Histopathol* 2013; 28: 15-21.
- [4] Fetissov F, Benatre A, Dubois MP, Lanson Y, Arbeille-Brassart B, Jobard P. Carcinoid tumor occurring in a teratoid malformation of the kidney. An immunohistochemical study. *Cancer* 1984; 54: 2305-8.
- [5] Lodding P, Hugosson J, Hansson G. Primary carcinoid tumour with ossification masquerading as calyx stone in a horseshoe kidney. *Scand J Urol Nephrol* 1997; 31: 575-8.
- [6] McVey RJ, Banerjee SS, Eyden BP, Reeve RS, Harris M. Carcinoid tumor originating in a horseshoe kidney. *In Vivo* 2002; 16: 197-99.
- [7] Armah HB, Parwani AV, Perepletchikov AM. Synchronous primary carcinoid tumor and primary adenocarcinoma arising within mature cystic teratoma of horseshoe kidney: a unique case report and review of the literature. *Diagn Pathol* 2009; 4: 17.
- [8] Resnick ME, Unterberger H, McLoughlin PT. Renal carcinoid producing the carcinoid syndrome. *Med Times* 1966; 94: 895-6.
- [9] Romero FR, Rais-Bahrami S, Permpongkosol S, Fine SW, Kohanim S, Jarrett TW. Primary carcinoid tumors of the kidney. *J Urol* 2006; 176: 2359-66.
- [10] Armah HB, Parwani AV. Primary carcinoid tumor arising within mature teratoma of the kidney: report of a rare entity and review of the literature. *Diagn Pathol* 2007; 2: 15.
- [11] Shelekhova KV, Hejda V, Kazakov DV, Michal M. Mature cystic teratoma of the ovary with male accessory sexual glands including seminal vesicles, prostatic tissue, and bulbo-urethral glands: a case report. *Virchows Arch* 2008; 452: 109-11.
- [12] Roma AA, Humphrey PA. Prostatic tissue in testicular teratoma. A clinicopathologic and immunohistochemical study. *Ann Diagn Pathol* 2013; 17: 10-3.
- [13] Jeung JA, Cao D, Selli BW, Clapp WL, Oliai BR, Parwani AV, Allan RW. Primary renal carcinoid tumors: clinicopathologic features of 9 cases with emphasis on novel immunohistochemical findings. *Hum Pathol* 2011; 42: 1554-61.
- [14] La Rosa S, Bernasconi B, Micello D, Finzi G, Capella C. Primary small cell neuroendocrine carcinoma of the kidney: morphological, immunohistochemical, ultrastructural, and cytogenetic study of a case and review of the literature. *Endocr Pathol* 2009; 20: 24-34.
- [15] Jimenez RE, Folpe AL, Lapham RL, Ro JY, O'Shea PA, Weiss SW, Amin MB. Primary Ewing's sarcoma/primitive neuroectodermal tumor of the kidney: a clinicopathologic and immunohistochemical analysis of 11 cases. *Am J Surg Pathol* 2002; 26: 320-7.
- [16] Hartman DJ, MacLennan GT. Renal metanephric adenoma. *J Urol* 2007; 178: 1058.