Pathol. Oncol. Res. (2010) 16:139–142
DOI 10.1007/s12253-009-9180-y

Primary Large Cell Neuroendocrine Carcinoma of the Kidney

Pavel Dundr · Michael Pešl · Ctibor Povýšil · Lenka Bauerová · Viktor Soukup

Received: 23 April 2009 / Accepted: 16 June 2009 / Published online: 7 July 2009

Abstract We report a case of a 56-year-old male with a primary large cell neuroendocrine renal carcinoma. Grossly, the left kidney was enlarged by a solid tumor that measured 145×125×100 mm. Histologically, the tumor consisted of large cells with a moderate to abundant amount of eosinophilic cytoplasm. The nuclei were irregular, some of them with finely or coarsely granular chromatin, others with vesicular chromatin and prominent nucleoli. The tumor cells showed multiple mitotic figures (up to 32 mitoses/10 HPF). In some areas, the tumor cells were arranged in solid sheets; however, the predominant pattern was solid-alveolar, trabecular and cribriform. Large areas of tumor necrosis were found. Immunohistochemically, the tumor cells were positive for synaptophysin, CD56 and CD57. Cytokeratin AE1/AE3, vimentin and CD10 were positive only focally. Chromogranin showed weak cytoplasmic positivity in rare tumor cells. Cytokeratin CAM5.2, cytokeratin 34βE12, BerEP 4, EMA, TTF-1, cytokeratin 7, cytokeratin 20, calretinin, serotonin, somatostatin, gastrin, calcitonin, glukagon and insulin were negative. Primary large cell neuroendocrine carcinoma of the kidney is a rare tumor. To the best of our knowledge, only 3 cases of a tumor of this type have been reported to date.

P. Dundr (✉) · C. Povýšil · L. Bauerová
Department of Pathology, 1st Faculty of Medicine and General Teaching Hospital, Charles University,
Studničkova 2,
Prague 128 00, Czech Republic
e-mail: pdundr@seznam.cz

M. Pešl · V. Soukup
Department of Urology, 1st Faculty of Medicine and General Teaching Hospital, Charles University,
Ke Karlovu 6,
Prague 128 00, Czech Republic

Keywords Carcinoma · Kidney · Large cell · Neuroendocrine · Renal tumors

Abbreviations
LCNC large cell neuroendocrine carcinoma

Introduction

Neuroendocrine tumors of the kidney are rare neoplasms that can be subdivided into epithelial and neural types [1, 2]. Neural types of neuroendocrine tumors of the kidney include primitive neuroectodermal tumor, neuroblastoma and paraganglioma [3, 4]. Epithelial types of neuroendocrine renal tumors include carcinoid tumor, small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma (LCNC) [2, 3]. Epithelial type of neuroendocrine renal tumors can arise in renal pelvis or renal parenchyma. The tumors arising in renal pelvis are usually associated with other types of tumors such as transitional cell carcinoma, adenocarcinoma and squamous cell carcinoma, whereas parenchymal tumors are mostly purely neuroendocrine [2, 5, 6]. Large cell neuroendocrine carcinoma of the kidney is a rare tumor, only 3 cases of this tumor were reported to date [1, 7]. We report an additional case of a primary pure large-cell neuroendocrine renal carcinoma that occurred in a 56-year-old male.

Case Report

A 56-year-old male visited his physician because of 4 months lasting left abdominal and lower back pain, weight loss (6 kg in the last 4 months) and digestive

symptoms including meteorism, flatulence and belching. Ultrasonography of the abdomen revealed a mass in the left kidney, and the patient was sent for urological examination. Computerized tomography (CT) scan showed a large tumor in the upper pole of the left kidney up to 14 cm in largest dimension. In addition, CT scan of the abdomen and thorax showed multiple liver metastases up to 4 cm in diameter and multiple bilateral lung metastases up to 1 cm in diameter. A transabdominal palliative nephrectomy was performed. Following the surgery the patient was referred to an oncological department in his regional hospital. A CT scan of the thorax and abdomen carried out 5 months after surgery revealed enlargement of the liver metastases up to 8.5 cm in diameter and increasing amount of bilateral lung metastases. The patient died 7 months after surgery. The autopsy was not performed.

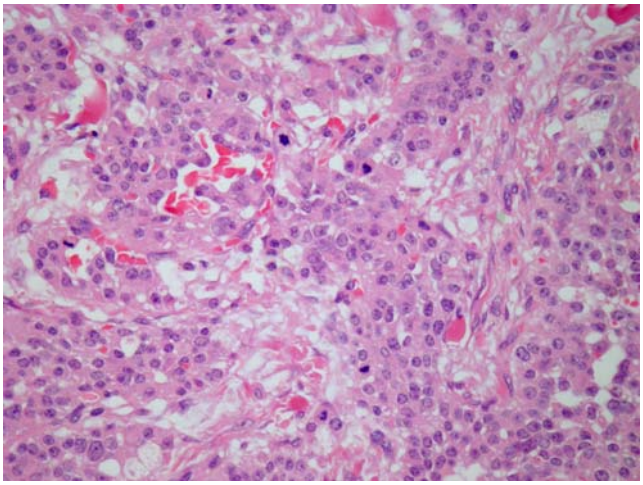

Fig. 1 Large tumor cells with irregular nuclei and multiple mitotic figures (H&E, 400x)

Materials and Methods

Sections from formalin-fixed, paraffin-embedded tissue blocks were stained with hematoxylin-eosin. Immunohistochemical staining was performed using the avidin-biotin complex method with antibodies directed against the following antigens: cytokeratin CAM5.2 (1:10, Becton-Dickinson, Mountain View, CA, USA), cytokeratin AE1/AE3 (1:50, Dako, Glostrup, Denmark), cytokeratin 34βE12 (1:10, Dako), calretinin (1:50, Dako), cytokeratin 7 (1:25, Dako), cytokeratin 20 (1:50, Dako), CD56 (1:50, Novocastra, Newcastle, UK), CD57 (1:50, Dako), synaptophysin (1:25, Dako), chromogranin A (1:50, Dako), EMA (1:100, Dako), vimentin (1:300, Bio Genex, San Ramon, CA, USA), CD 10 (1:30, NeoMarkers, Fremont, CA, USA), calcitonin (1:400, Dako), gastrin (1:40, Sigma, St. Louis, MO, USA), glukagon (1:2,000, Sigma), insulin (1:1,000, Dako), serotonin (1:10, Dako), somatostatin (1:200, Dako), TTF-1 (1:100, NeoMarkers) and MIB-1 (1:50, Dako).

Results

Grossly, the resected specimen consisted of the left kidney with part of the ureter, and perirenal fat without adrenal gland. Most of the left kidney was replaced by a tumor, which grew partly exophytically in the upper pole. There was apparent an extracapsular spread and the tumor grew into the peripelvic and perinephric fat. In cross section, the tumor was light gray with multiple yellow foci.

Microscopically, multiple sections of different areas of the tumor showed the same histological pattern. The tumor consisted of large cells with a moderate to abundant amount of eosinophilic cytoplasm (Fig. 1). The nuclei were irregular, some of them with finely or coarsely granular chromatin, others with vesicular chromatin and prominent nucleoli. The tumor cells showed multiple mitotic figures (up to 32 mitoses/10 HPF). Some of the mitoses were atypical. In some areas, the tumor cells were arranged in solid sheets (Fig. 2); however, the predominant pattern was solid-alveolar, trabecular, pseudoglandular and cribriform (Fig. 3). Large areas of tumor necrosis were found. The angioinvasion and extracapsular spread were present.

Immunohistochemically, the tumor cells were positive for synaptophysin (Fig. 4), CD56 and CD57. Cytokeratin AE1/AE3, vimentin and CD10 were positive only focally. Chromogranin showed weak cytoplasmic positivity in rare tumor cells. Cytokeratin CAM5.2, cytokeratin 34βE12, BerEP 4, EMA, TTF-1, cytokeratin 7, cytokeratin 20, calretinin, serotonin, somatostatin, gastrin, calcitonin, glukagon and insulin were negative. Examination of prolifer-

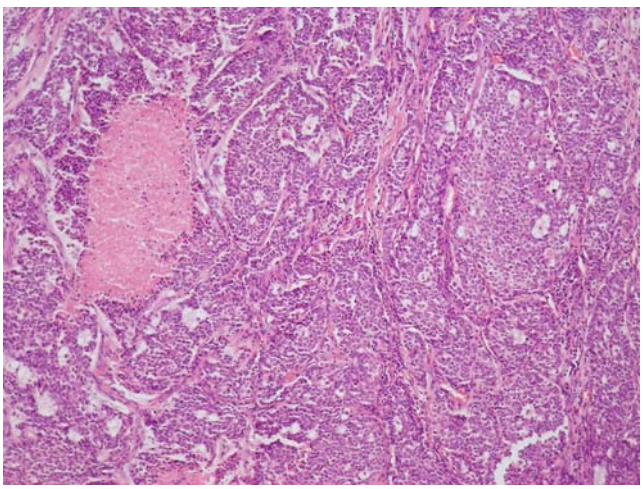

Fig. 2 Tumor cells arranged in solid sheets and irregular nests. Note the focal cribriform and pseudoglandular pattern (H&E, 200x)

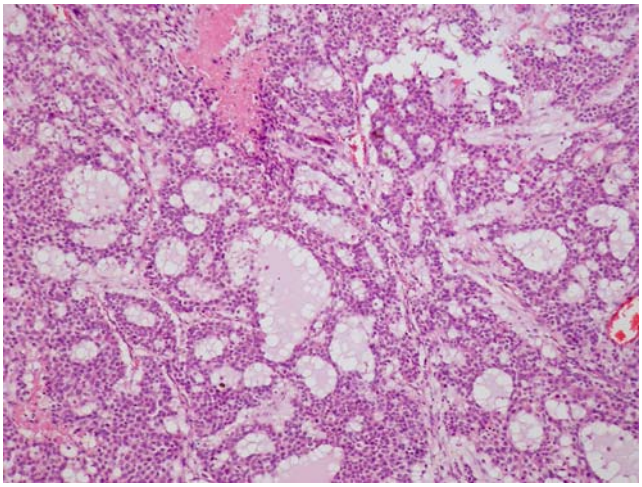

Fig. 3 Tumor cells arranged in pseudoglandular and cribriform pattern (H&E, 200x)

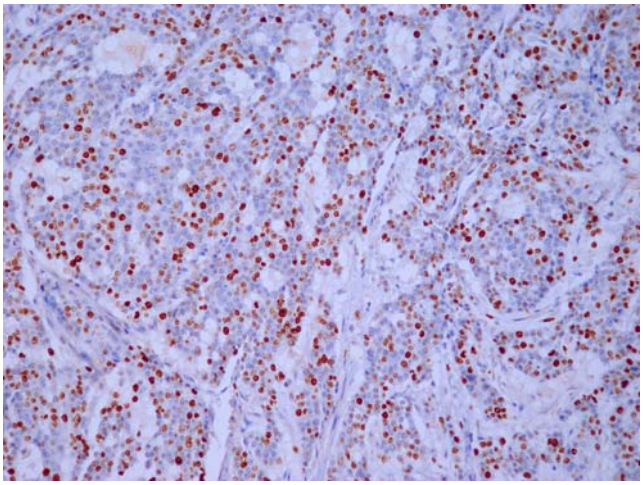

Fig. 5 Nuclear positivity for MIB-1 in about 60% of tumor cells (200x)

ative activity with monoclonal antibody MIB-1 showed nuclear positivity in about 60% of tumor cells (Fig. 5).

Discussion

Neuroendocrine tumors of the kidney are rare neoplasms that can be subdivided into epithelial and neural types [1, 2]. Epithelial type of neuroendocrine renal tumors include carcinoid tumor, small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma [1, 2]. Neural types of neuroendocrine tumors of the kidney include primitive neuroectodermal tumor, neuroblastoma and paraganglioma [3, 4]. Epithelial type of neuroendocrine renal tumors can arise in renal pelvis or renal parenchyma. The tumors arising in renal pelvis are usually associated with other types of tumors such as transitional cell carcinoma, adenocarcinoma and squamous cell carcinoma, whereas parenchymal tumors are mostly purely neuroendocrine [2, 5, 6]. One report described neuroendocrine tumor arising in renal parenchyma associated with a chromophobe renal cell carcinoma [8]. Moreover, neuroendocrine differentiation was described in mucinous tubular and spindle cell carcinoma [9, 10].

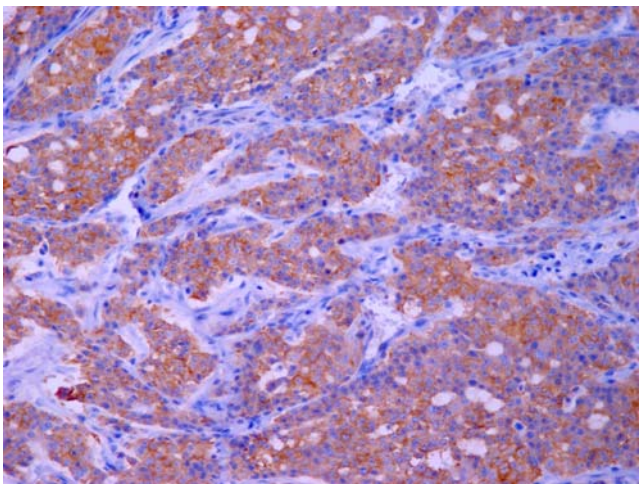

Fig. 4 Tumor cells positivity for synaptophysin (400x)

About 90 cases of primary carcinoid tumor of the kidney have been reported in the literature to date; mostly as case reports or small case series [1, 11-13]. Only one large series of 21 cases has recently been reported [14]. Primary renal carcinoid tumor could arise in horseshoe kidney (18–26%) or be associated with renal teratomas (≈ 15%) [11, 12, 15]. Patients with renal carcinoid frequently present with regional lymph node or distant metastases; however, usually have a prolonged clinical course despite the metastatic disease [2, 14]. The pathogenesis of renal carcinoid tumors remains uncertain. The most popular hypothesis is that these tumors arise from a primitive totipotential cell line that differentiates in a neuroendocrine direction [2].

About 40 cases of small cell neuroendocrine carcinoma have been reported in the literature to date [6, 15-22]. These tumors are very aggressive with early metastatic spread and at least 75% of patients die of the disease within a year after the diagnosis [2, 6]. In addition, three cases of LCNC have been reported to date, one of them in English and another two in French language literature [1, 7]. The behavior of all three reported cases of renal LCNC as well as our case seems to be similar to small cell carcinoma. The tumors presented in advanced stage and all patients died of the disease within 7 months after the diagnosis.

Histologically, large-cell neuroendocrine carcinoma of the kidney is similar to LCNC of other organs. The tumor cells are large with a moderate amount to abundant

cytoplasm and large nuclei, some of them with granular and other vesicular chromatin with prominent nucleoli. Mitotic activity is brisk and necroses are a common finding. The tumor cells are usually arranged in solid nests, sheets or trabeculae and cribriform formations can be found. Immunohistochemically, the tumors express at least some of the neuroendocrine markers including synaptophysin, chromogranin, NSE and CD56.

The differential diagnosis of renal large cell neuroendocrine carcinoma includes primary or metastatic neuroendocrine tumors including carcinoid, small cell neuroendocrine carcinoma and Merkel cell carcinoma [23]. In contrast to LCNC, primary or metastatic carcinoid has a low mitotic index, cytological uniformity, an organoid architectural pattern, and absent necrosis. Primary and metastatic small cell neuroendocrine carcinomas are characterized by a smaller cell size; however, scattered large cells can be found. In the cases of mixed neuroendocrine and other types of tumors we should be aware of the possibility of tumor-to-tumor metastasis. These cases are rare; however, renal cell carcinoma is the most common recipient of tumor-to-tumor metastasis in malignant tumors [24]. Moreover, metastases of neuroendocrine carcinoma were described into other types of renal tumors such as angiomyolipoma [25].

In conclusion, we described an additional case of large-cell neuroendocrine carcinoma of the kidney. Despite its rarity, this tumor should be regarded in the differential diagnosis of primary and metastatic renal neuroendocrine tumors. LCNC of the kidney seems to be an aggressive tumor that has a poor prognosis; however, the number of reported cases is too small and the study of more cases will be necessary for assessing the biological behavior and the factors with a potential influence on the prognosis of these tumors.

Acknowledgement This work was supported by Ministry of Education Research Project MSM0021620808.

References

1. Lane BR, Chery F, Jour G et al (2007) Renal neuroendocrine tumours: a clinicopathological study. BJU Int 100:1030–1035
2. Mazzucchelli R, Morichetti D, Lopez-Beltran A et al (2009) Neuroendocrine tumours of the urinary system and male genital organs: clinical significance. BJU Int. Feb 27. [Epub ahead of print]
3. Lagace R, Tremblay M (1968) Non-chromaffin paraganglioma of the kidney with distant metastases. Can Med Assoc J 99:1095–1098
4. Sellaturay SV, Arya M, Banisadr S et al (2006) Primary intrarenal neuroblastoma: A rare, aggressive tumour of childhood mimicking Wilms' tumour. J Pediatr Urol 2:522–524
5. Guillou L, Duvoisin B, Chobaz C et al (1993) Combined small-cell and transitional cell carcinoma of the renal pelvis. A light microscopic, immunohistochemical, and ultrastructural study of a case with literature review. Arch Pathol Lab Med 117:239–243
6. La Rosa S, Bernasconi B, Micello D et al (2008) Primary Small Cell Neuroendocrine Carcinoma of the Kidney: Morphological, Immunohistochemical, Ultrastructural, and Cytogenetic Study of a Case and Review of the Literature. Endocr Pathol 20:24–34
7. Moukassa D, Leroy X, Bouchind'homme B et al (2000) Primary large cell neuroendocrine carcinoma of the kidney: morphologic and immunohistochemical features of two cases. Ann Pathol 20:357–360
8. Parada DD, Peña KGB (2008) Chromophobe renal cell carcinoma with neuroendocrine differentiation. APMIS 116:859–865
9. Kuroda N, Hes O, Miyazaki E et al (2006) Frequent expression of neuroendocrine markers in mucinous tubular and spindle cell carcinoma of the kidney. Histol Histopathol 21:7–10
10. Kuroda N, Nakamura S, Miyazaki E et al (2004) Low-grade tubular-mucinous renal neoplasm with neuroendocrine differentiation: a histological, immunohistochemical and ultrastructural study. Pathol Int 54:201–207
11. Armah HB, Parwani AV (2007) Primary carcinoid tumor arising within mature teratoma of the kidney: report of rare entity and review of the literature. Diagn Pathol 2:15
12. Boix Orri R, Mora Durban MJ, Sánchez Macías J et al (2008) Neuroendocrine tumor in a horseshoe kidney: relative risk of association of two related entities. Arch Esp Urol 61:819–822
13. Romero FR, Rais-Bahrami S, Permpongkosol S et al (2006) Primary carcinoid tumors of the kidney. J Urol 176:2359–2366
14. Hansel DE, Epstein JI, Berbescu E et al (2007) Renal carcinoid tumor: a clinicopathologic study of 21 cases. Am J Surg Pathol 31:1539–1544
15. Chung CH, Park CY (2006) Small cell carcinoma of the kidney. Korean J Intern Med 21:191–193
16. Capella C, Eusebi V, Rosai J (1984) Primary oat cell carcinoma of the kidney. Am J Surg Pathol 8:855–861
17. González-Lois C, Madero S, Redondo P et al (2001) Small cell carcinoma of the kidney: a case report and review of the literature. Arch Pathol Lab Med 125:796–798
18. Kilicarsalan Akkaya B, Mustafa U, Esin O et al (2003) Primary small cell carcinoma of the kidney. Urol Oncol 21:11–13
19. Kitamura M, Miyanaga T, Hamada M et al (1997) Small cell carcinoma of the kidney: case report. Int J Urol 4:422–424
20. Masuda T, Oikawa H, Yashima A et al (1998) Renal small cell carcinoma (neuroendocrine carcinoma) without features of transitional cell carcinoma. Pathol Int 48:412–415
21. Morgan KG, Banerjee SS, Eyden BP (1996) Primary small cell neuroendocrine carcinoma of the kidney. Ultrastruct Pathol 20:141–144
22. Tetu B, Ro JY, Ayala AG et al (1987) Small cell carcinoma of the kidney. Cancer 60:1809–1814
23. Pollheimer VS, Bodo K, Pollheimer MJ et al (2007) Merkel cell carcinoma metastasizing to the kidney mimicking primary neuroendocrine renal cancer. APMIS 115:774–777
24. Ulamec M, Tomas D, Perić-Balja M et al (2008) Neuroendocrine breast carcinoma metastatic to renal cell carcinoma and ipsilateral adrenal gland. Pathol Res Pract 204:851–855
25. Ricketts R, Tamboli P, Czerniak B et al (2008) Tumor-to-tumor metastasis: report of 2 cases of metastatic carcinoma to angiomyolipoma of the kidney. Arch Pathol Lab Med 132: 1016–1020