

Review

Review of renal carcinoid tumor with focus on clinical and pathobiological aspects

Naoto Kuroda¹, Azusa Tanaka¹, Chisato Ohe², Shuji Mikami³, Yoji Nagashima⁴, Keiji Inoue⁵, Taro Shuin⁵, Takahiro Taguchi⁶, Akira Tominaga⁶, Isabel Alvarado-Cabrero⁷, Fredrik Petersson⁸, Matteo Brunelli⁹, Guido Martignoni⁹, Michal Michal¹⁰ and Ondrej Hes¹⁰

¹Department of Diagnostic Pathology, Kochi Red Cross Hospital, ²Department of Surgical Pathology, Kansai Medical University Hirakata Hospital, ³Division of Diagnostic Pathology, Keio University Hospital, Tokyo, Japan, ⁴Department of Molecular Pathology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, ⁵Department of Urology, Kochi Medical School, Kochi University, Kochi, Japan, ⁶Division of Human Health and Medical Science, Graduate School of Kuroshio Science, Kochi University, Kochi, Japan, ⁷Department of Pathology, Mexican Oncology Hospital, Mexico City, Mexico, ⁸Department of Pathology, National University Hospital System, Singapore, Singapore, ⁹Department of Pathology, University of Verona, Verona, Italy and ¹⁰Sikl's Department of Pathology, Charles University Medical Faculty Hospital, Plzen, Czech Republic

Summary. Renal carcinoid tumor is a rare neoplasm. In this article, we review this neoplasm with a focus on clinical and pathobiological aspects. The majority of patients present in the fourth to seventh decades, but there is no gender predilection. Clinically, patients with renal carcinoid tumor frequently present with abdominal, back or flank pain. This tumor is occasionally associated with horseshoe kidney and/or mature cystic teratoma located in the kidney. Macroscopically, these tumors are well demarcated with a lobulated appearance and yellow or tan-brown color cut surface. Microscopically, these tumors are composed of monomorphic round to polygonal cells with granular amphophilic to eosinophilic cytoplasm. Tumor cells are arranged in trabecular, ribbon-like, gyriform, insular, glandular and solid patterns. The nuclei are round to oval and with evenly distributed nuclear chromatin, frequently with a “salt and pepper”-pattern. Immunohistochemically, tumor cells demonstrate immunolabeling for chromogranin A and synaptophysin. Ultrastructurally, the neoplastic cells contain abundant dense core neurosecretory granules. In previous genetic studies, abnormalities of chromosomes 3 or 13 have been reported. The clinical behavior of renal carcinoid tumors is variable, but is more indolent than most renal cell carcinomas. Further investigations are warranted in order to elucidate the critical genetic abnormalities

responsible for the pathogenesis of this rare entity in renal neoplastic pathology.

Key words: Renal carcinoid tumor, Pathology, Chromosome 3/13

Introduction

Renal neuroendocrine tumors are rare neoplasms which are currently classified into four categories; (1) typical carcinoid, (2) atypical carcinoid, (3) small cell carcinoma and (4) large cell neuroendocrine carcinoma (Lane et al., 2007, 2009). Atypical carcinoid is much rarer than typical carcinoid (Gunes et al., 2002; Quinchon et al., 2003; Romero et al., 2006; Hansel et al., 2007; Jeung et al., 2011). As it is very difficult to distinguish carcinoid tumor arising in the renal parenchyma from that in renal pelvis, these tumors have been grouped together in a recent review article (Ji and Li, 1994; Rudrick et al., 1995; Murali et al., 2006; Kuroda et al., 2008, 2010). According to the most recent WHO classification, the classification of neuroendocrine neoplasms in all organs seems to be subdivided into well differentiated neuroendocrine tumor (carcinoid), well differentiated neuroendocrine carcinoma (atypical carcinoid) and poorly differentiated neuroendocrine carcinoma (small cell- and large cell neuroendocrine carcinoma).

In this article, we present an overview of the subsets of well differentiated renal neoplasms, including typical

and atypical, with an emphasis on clinical and pathobiological aspects.

Clinical characteristics

Although the age-range of patients is wide (range; 13-68 years; mean; 47 years, Murali et al., 2006), the majority present in the fourth to seventh decades. There is no gender predilection (Murali et al., 2006). Not infrequently, this tumor occurs in patients younger than 50 years of age. Clinically, patients with renal carcinoid tumor frequently present with abdominal, back or flank pain, and/or an enlarging abdominal mass. Fullness, weight loss, hematuria and anemia may be observed (Gunes et al., 2002; Kawajiri et al., 2004; Murali et al., 2006; Hansel et al., 2007; Geramizadeh et al., 2009). A significant number of cases, reportedly up to 28.6%, have clinically silent tumors that are incidentally detected (Romero et al., 2006). Renal carcinoid tumors have been associated with horseshoe kidney (18-26%), mature cystic teratoma (15%), polycystic kidney disease (2%) or renal dysplasia (Kojiro et al., 1976; Fetissov et al., 1984; Acconcia et al., 1988; Machet et al., 1994; van den Berg et al., 1995; Kurl et al., 1996; Krishnan et al., 1997; Begin et al., 1998; Isobe et al., 2000; McVey et al., 2002; Yoo et al., 2002; Murali et al., 2006; Hansel et al., 2007; Armah and Parwani, 2007; Rodriguez-Covarrubias et al., 2007; Armah et al., 2009). A case of synchronous primary carcinoid tumor and primary adenocarcinoma arising in mature cystic teratoma in a horseshoe kidney has also been reported (Armah et al., 2009). The majority of cases with this tumor do not have any evidence of carcinoid syndrome, but cases with functional syndrome are on record (Resnick et al., 1966; Hannah et al., 1988; Takeshima et al., 1996; Romero et al., 2006; Lane et al., 2007).

Imaging findings

There are no specific radiological features that discriminate renal carcinoid tumor from renal cell carcinoma (RCC) (Moulopoulos et al., 1991; Lane et al., 2009; Singh et al., 2009). Ultrasound sonography reveals hyperechoic mass (Moulopoulos et al., 1991). Computed tomography scan and magnetic resonance imaging demonstrate a well-defined mass with cystic change or focal calcification in occasional cases (Murali et al., 2006). Angiography discloses a variable, avascular, hypovascular or hypervascular mass (McKeown et al., 1988; Moulopoulos et al., 1991; Murali et al., 2006; Jain et al., 2010; Kato et al., 2010). One case with inferior vena caval tumor thrombus radiologically detected has been reported (Szymanski et al., 2009).

Pathological findings

Macroscopic findings

Broadly, renal carcinoid tumors are well circumscribed with a lobulated contour and the cut surface of this neoplasm demonstrates a yellow to tan-brown color (Lane et al., 2009; Kuroda et al., 2010). Focal cystic change, hemorrhage and calcification may be observed (Toker, 1974). These tumors may occur in both the renal parenchyma as well as in the renal pelvis (Murali et al., 2006).

Microscopic findings

Histologically, renal carcinoid tumors are composed of monomorphic, round to polygonal cells with granular amphophilic to eosinophilic cytoplasm. Tumor cells are arranged in trabecular, ribbon-like, gyriform, insular,

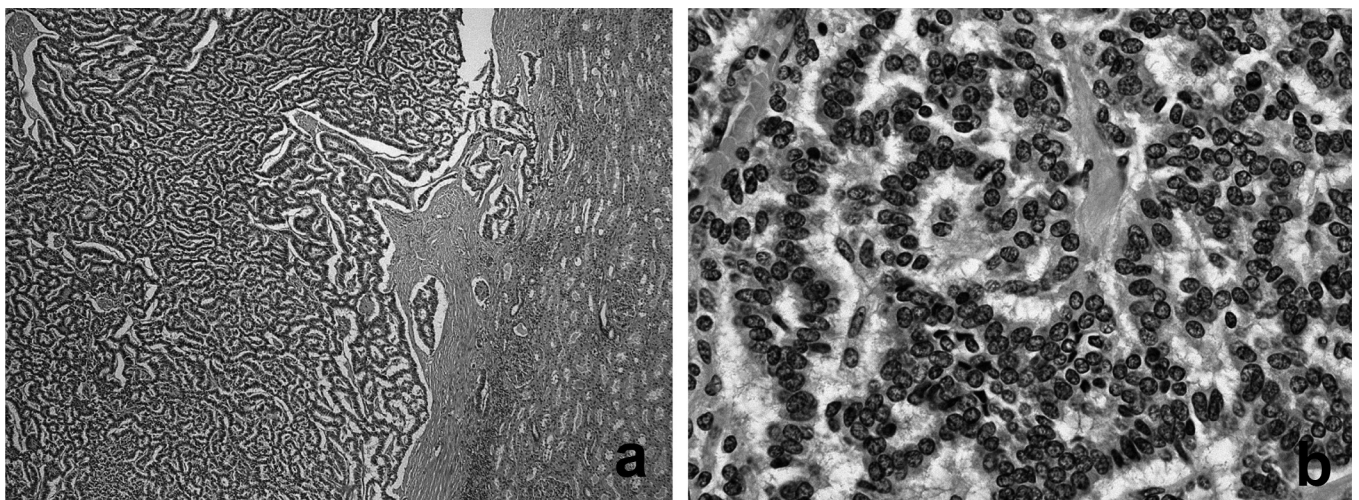


Fig. 1. Microscopic findings. **a.** Low magnification. Tumor cells are arranged in trabecular pattern. **b.** High magnification. Nuclei are round and the nuclear chromatin shows a salt and pepper pattern. a, x 20; b, x 200

glandular and solid patterns (Murali et al., 2006; Kuroda et al., 2010) (Fig. 1a). The nuclei are monomorphic; round to oval with evenly distributed chromatin which has been characterized as “salt and pepper pattern” (Fig. 1b). Nucleoli are absent to inconspicuous. Mitotic figures are sparse and mitotic activity is generally less than 6 mitotic figures per 10 high power fields. Focal calcification or metaplastic ossification may be present in the stroma (Armah et al., 2009; Singh et al., 2009). Necrosis is generally absent. Perinephric fat invasion is not uncommonly seen. Lymphovascular invasion may be observed. If necrotic foci and/or high number of mitotic figures (more than 2 mitotic figures per 10 high power fields) are identified, a diagnosis of atypical carcinoid should be rendered (Quinchon et al., 2003; Jeung et al., 2011).

Histochemical findings

Argyrophil stain, such as Grimelius, frequently highlights the cytoplasmic neurosecretory granules in the tumor cells (Sahin et al., 1996; Murali et al., 2006; Kuroda et al., 2010).

Immunohistochemical findings

The neoplastic cells are, to varying degrees, immunoreactive with neuron specific enolase (NSE), chromogranin A (Fig. 2), synaptophysin, Leu-7, CD56 and cytokeratin CAM5.2 (Sahin et al., 1996; Hansel et al., 2007; Murali et al., 2006; Kuroda et al., 2008, 2010; Jeung et al., 2011). CD99 is expressed in the majority of cases of carcinoid tumor (Jeung et al., 2011). Neoplastic cells are usually negative for thyroid transcription factor-1 and WT1 (Hansel et al., 2007; Jeung et al., 2011). The

renal-associated transcription factors, including airer box gene 2 (PAX2) and paired box gene 8 (PAX8), are consistently negative (Jeung et al., 2011).

Ultrastructural findings

Numerous membrane-bound and round dense core granules with peripheral lighter zones, ranging in size from 100 to 400 nm, corresponding to neurosecretory granules, are observed in the cytoplasm of the neoplastic cells (Fig. 3) (Ghazi et al., 1979; Stahl and Sidhu, 1979; McDonald et al., 1983; Zak et al., 1983; Acconcia et al., 1988; Huettner et al., 1991; Goldblum and Lloyd, 1993; Masera et al., 1993; Schluskel et al., 1993; Murali et al., 2006; Kuroda et al., 2008; Jain et al., 2010). Neurosecretory granules may show the polar distribution (Zak et al., 1983; Acconcia et al., 1988; Huettner et al., 1991). Moreover, neoplastic cells may contain lipid droplets, intermediate filaments, thin microfilaments, tonofilament bundles, mitochondria and endoplasmic reticulum (Acconcia et al., 1988; Cauley et al., 1988; Huettner et al., 1991; Ovcak et al., 1992).

Molecular genetic findings

Data on molecular genetic changes in renal carcinoid tumors are scarce. One renal carcinoid tumor showed a karyotype of 47, XX, +13[8]/46, XX, t(13;14)(q31;q11.2)[5]/46, XX[2] (van den Berg et al., 1995). The author concluded that numerical and structural aberrations of chromosome 13 may play a crucial role in the development of metanephric-derived renal tumors. Loss of heterozygosity (LOH) at the D3F15S2 (3p21 telomeric) was observed in another case (El-Naggar et al., 1995). In fluorescence *in situ* hybridization study,

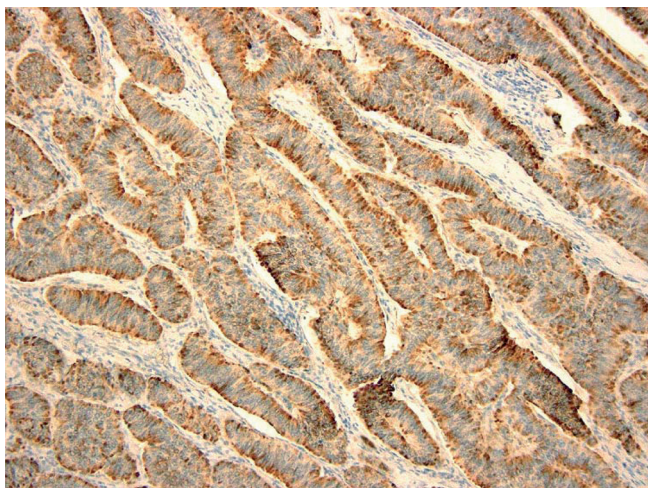


Fig. 2. Immunohistochemical findings. The neoplastic cells are positive for chromogranin A.

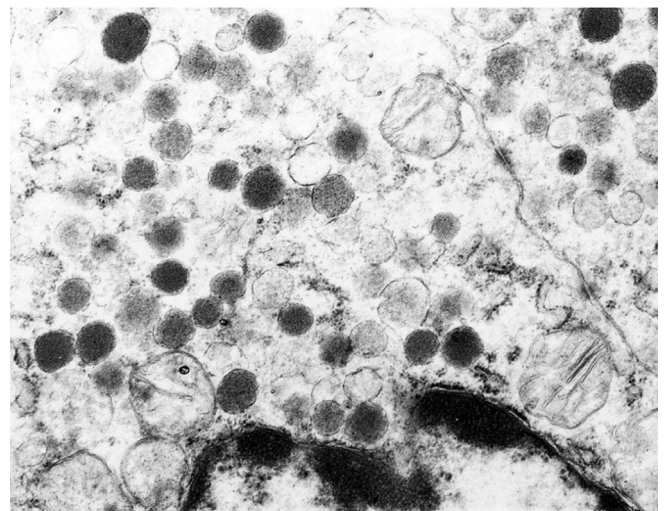


Fig. 3. Ultrastructural findings. The cytoplasm of tumor cells contains dense core granules with peripheral lighter zone. x 1,000

three of four tumors showed monosomy of chromosome 3 (D3Z1), but one tumor demonstrated monosomy of chromosome 13 (D13S319/13q34). Using PCR amplification and fragment analysis of three microsatellite markers (D3S1300, D3S666 and D3S1768) of chromosome arm 3p, one tumor exhibited LOH at D3S1300 and D3S1768 (Kuroda et al., 2010). Using comparative genomic hybridization, we recently found gains of chromosome 1q and losses of chromosomes 3 and Y in one male patient with a renal carcinoid tumor arising in horseshoe kidney (Fig. 4)

Differential diagnosis

The renal carcinoid tumor should be distinguished from metastatic carcinoid derived from other anatomic sites, including the digestive and respiratory tract (Tal et al., 2003; Kato et al., 2010). In addition, small cell carcinoma, large cell neuroendocrine carcinoma, primitive neuroectodermal tumor (PNET)/Ewing sarcoma, renal carcinoma with t(6;11)(p21;q12-13) and small cell oncocyoma with pseudorosettes (SCOP) and chromophobe renal cell carcinoma with neuroendocrine differentiation need to be distinguished from renal carcinoid tumors. Of note is that carcinoid tumors arising in the gastrointestinal- and respiratory tract are far more common than those arising in the urogenital system. Accordingly, whenever the diagnosis of renal carcinoid tumor is made, a systemic search for a possible primary elsewhere should be diligently performed (Juma

et al., 1989). Renal small cell carcinoma is histologically identical to its pulmonary counterpart and consists of small cells, with two to three times of small lymphocytes in size, with scant cytoplasm, nuclear hyperchromasia with fine (non-coarse) chromatin, frequently nuclear moulding and small to inconspicuous nucleoli (Tetu et al., 1987; Gonzalez-Lois et al., 2001). In PNET/Ewing sarcoma, Small, blue tumor cells are arranged in sheets, cords or rosette formations with central fibrillary material. PNET/Ewing sarcoma shows strong immunoreactive for CD99 and Fli-1. It is important to note in this respect that renal carcinoid tumors frequently display immunoreactivity for CD99. In difficult cases, eg. with limited biopsy material, the identification of a chimeric transcript specific for PNET/Ewing sarcoma may be very useful (Marley et al., 1997; Sheaff et al., 1997). The exceedingly rare renal carcinoma/tumor with t(6;11)(p21;q12-13), also shows a small cell component. However, in this tumor, the small (lymphocyte-like) tumor cells are different (smaller) from those seen in renal carcinoid tumors and they form (pseudo-)rosette-like arrangements around small globules composed of basement membrane material (Argani et al., 2005; Petersson et al., 2012). Another entity that needs to be distinguished from renal carcinoid tumor is the renal small cell oncocyoma with pseudorosette (SCOP), which focally may show overlapping histological features with renal carcinoid tumor. This uncommon and unique variant of renal oncocyoma was recently comprehensively characterized by Petersson et al. (2011). In addition, it is important to recognize that chromophobe renal cell carcinoma rarely show neuroendocrine differentiation (Kuroda et al., 2011). Based on previous data on renal carcinoid tumor, the presence of horseshoe kidney or a mature cystic teratoma in the kidney would be supportive of the diagnosis of renal carcinoid tumor.

Suggested origin

The histogenesis of renal carcinoid tumor is uncertain. Neuroendocrine cells are not identified in the normal kidney (Begin, 1996). We suggest that renal carcinoid tumor is not derived from native renal elements because renal-associated transcription factors are constantly negative in this tumor group (Jeung et al., 2011). Most investigators have postulated that renal carcinoid tumor originates from multipotential primitive stem cells capable of neuroendocrine differentiation (Unger et al., 1990; Raslan et al., 1993; Rudrick et al., 1995; Lodding et al., 1997; Yoo et al., 2002). Additionally, it has been also proposed that neural crest can be entrapped in the kidney during embryogenesis or renal pelvic cells undergo intestinal metaplasia and this epithelium subsequently show neuroendocrine differentiation (Yoo et al., 2002; Murali et al., 2006). It is possible that some tumors may originate from intestinal or bronchial epithelium in teratoma component (Yoo et al., 2002; Murali et al., 2006).

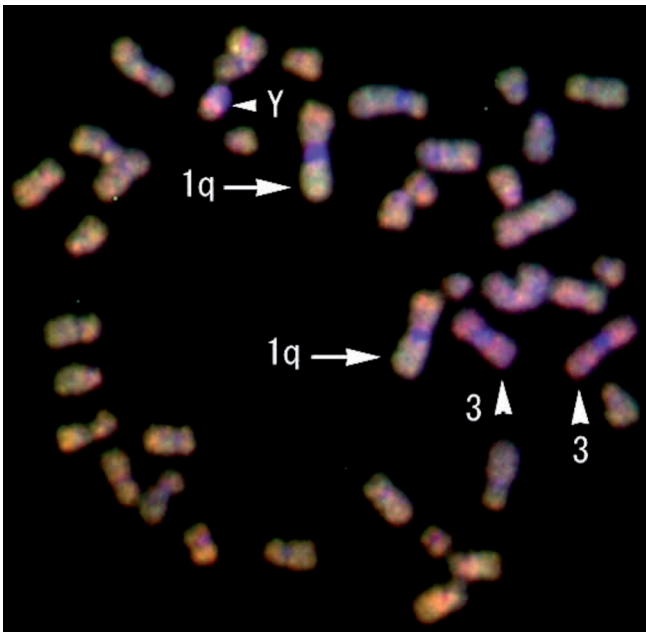


Fig. 4. Comparative genomic hybridization findings. Gains of chromosome 1q (arrows) and losses of chromosomes 3 (arrowheads) and Y (arrows) are observed.

Therapy

As renal carcinoid tumors may behave in a malignant fashion, including invasive growth, i.e. perinephric fat invasion and regional lymph node metastases, this tumor needs to be managed by radical nephrectomy with retroperitoneal lymphadenectomy (Juma et al., 1989). The option of partial nephrectomy for organ-confined disease may be considered (Shurtleff et al., 2005). However, the role for nephron-sparing surgery has yet to be determined. Renal carcinoid tumors appear to be resistant to chemotherapy (Raslan et al., 1993).

Prognosis

Although renal carcinoid tumor is a malignant tumor, it generally shows, in contrast to small cell- and large cell neuroendocrine carcinoma (which are both associated with poor clinical outcome), a more indolent, albeit variable clinical behavior (Cauley et al., 1988; Lane et al., 2007). In line with its low-grade malignant nature, the spectrum of biological behavior is more indolent than RCC (Jain et al., 2010). However, patients with renal carcinoid tumor may present with metastasis to regional lymph nodes and there may be progression to distant organ metastasis, including liver, lung and bone (Ghazi et al., 1979; Cauley et al., 1988; Mouloupoulos et al., 1991; Ovcak et al., 1993; Schluskel et al., 1993; Kurl et al., 1996; Murali et al., 2006; Hansel et al., 2007). Importantly (and in line with its low-grade biological behavior), despite widely metastatic disease, patients tend to have a prolonged clinical course (Shurtleff et al., 2005; Murali et al., 2006; Hansel et al., 2007; Gedaly et al., 2008). A case of atypical carcinoid showing a prolonged natural history without any medical intervention or follow-up for ten years has been reported (Gunes et al., 2002). Reportedly, poor prognostic factors include (1) age older than 40 years, (2) tumor size greater than 4 cm, (3) purely solid tumor (cut surface), (4) mitotic rate higher than 1/10 high power fields, (5) metastasis at the initial diagnosis and (6) tumors extending throughout the renal capsule (Shurtleff et al., 2005; Romero et al., 2006). Interestingly, primary carcinoid tumor arising in horseshoe kidney seems to be more indolent than those in non-horseshoe kidney (Isobe et al., 2000).

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