Summary. Renal oncocytois is a recently established disease entity characterized by numerous oncocyty tumors and diffuse involvement of oncocyty changes in renal parenchymal epithelia. In this article, we review this disease with a focus on its clinical and pathobiological aspects. Clinically, renal oncocytois may occur in a sporadic form without any underlying disease or may be associated with chronic renal failure/long-term hemodialysis. However, Birt-Hogg-Dubé syndrome, characterized by skin tumors such as fibrofolliculoma or trichodiscoma, pulmonary lesions including bullae and spontaneous pneumothorax, and renal tumors should be evaluated in the differential diagnosis. The disease can develop either unilaterally or bilaterally. The involved renal parenchyma contains several to multiple brownish-colored nodules of varying size and is entirely replaced by lesions at the overt stage. Histologically, oncocyty tumors in both the dominant mass and smaller lesions encompass so-called hybrid tumor, chromophobe renal cell carcinoma (RCC), and renal oncocytoa (RO). Regarding renal parenchymal abnormalities, infiltrative growth of oncocyty cells, cortical cysts with oncocyty features, or extensive oncocyty change in non-neoplastic tubules can also be observed. Histochemical, immunohistochemical, and molecular genetic features of chromophobe RCC and RO arising in the setting of renal oncocytois are generally identical to those in the sporadic type. However, hybrid tumors seem to be histologically distinct from chromophobe RCC and RO. In FISH analyses of some hybrid tumors, a gain of chromosomes 1, 2, 6, 10, and 17 was identified. In one tumor, no germ line mutation of folliculin gene was identified. Published data show that tumors follow a benign course. Further studies will be necessary to clarify the pathogenesis of renal oncocytois.

Key words: Renal oncocytois, Hybrid tumor, Chromophobe renal cell carcinoma, Oncocytoa

Introduction

Renal oncocytoa (RO) is a benign renal neoplasm constituting approximately 5-7% of all renal tumors. It is multifocal in 5-13% and bilateral in 2.5-5% of cases (Amin et al., 1997; Perez-Ordonez et al., 1997; Dechet et al., 1999; Kuroda et al., 2003a,b; Trpkov et al., 2010). Warfel and Eble (1982) described a case with multiple ROs (>200 tumors) and termed it as “renal oncocytyomas”; similar cases have been described to date (Sydor et al., 2009). Several years later, Tickoo et al. (1999) used the term “oncocytosis” to describe an almost identical lesion, and this term has been widely accepted since then. Renal oncocytois is defined as diffuse replacement of the renal parenchyma by numerous oncocyty tumors, such as hybrid tumor, chromophobe renal cell carcinoma (RCC), and RO, and oncocyty change in non-neoplastic renal parenchyma (Tickoo et al., 1999). Pathogenetically, this disease may arise sporadically in patients with chronic renal failure/long-term hemodialysis or in association with Birt-Hogg-Dubé syndrome.
Dubé (BHD) syndrome (Tickoo et al., 1999; Leroy et al., 2001; Shiga et al., 2002; Kuroda et al., 2003; Dimashkieh et al., 2004; Nagashima et al., 2005; Mazzucchelli et al., 2008). In this article, we present an overview of renal oncocytosis without any fundamental disease or chronic renal failure/long-term hemodialysis.

Clinical characteristics

Patients with renal oncocytosis were aged between 34 and 86 years (mean, 63.6 years; median, 62.5 years), and the male:female ratio was 2:5 (Tickoo et al., 1999). However, a case of childhood renal oncocytosis has also been described (Chen et al., 2003). Several cases associated with papillary adenoma, clear cell RCC, papillary RCC, and malignant lymphoma have been reported (Menendez et al., 2007; Mazzucchelli et al., 2008; Martín Martín et al., 2010). Some patients were incidentally found to have a renal abnormality, whereas others presented with microscopic hematuria or abdominal pain (Ariaratnam et al., 2008; Mazzucchelli et al., 2008).

Imaging findings

Ultrasonography can detect dominant masses, but smaller lesions may fail to be visualized. However, contrast-enhanced computed tomography (CT) imaging may demonstrate numerous hypovascular, homogenous renal masses. In patients with renal failure, magnetic resonance imaging may be a safe and effective alternative to CT for initial diagnosis and postoperative surveillance (Ariaratnam et al., 2008).

Pathological findings

Macroscopic findings

Generally, several tumors involving the kidney either unilaterally or bilaterally are found (Fig. 1). The cut surface of the tumors appears brown to mahogany-brown (Leroy et al., 2001; Dimashkieh et al., 2004; Nagashima et al., 2005). The size of dominant masses is 2.0-10.5 cm (Tickoo et al., 1999), and smaller lesions may frequently be detectable on gross inspection (Tickoo et al., 1999; Leroy et al., 2001; Chen et al., 2003; Dimashkieh et al., 2004; Nagashima et al., 2005).

Microscopic findings

Histologically, the dominant mass shows the features of RO, hybrid tumor, or chromophobe RCC. RO is characterized by a nested, acinar, tubular, or tubulocystic growth pattern with edematous to hyalinized stroma. Cytologically, centrally located round the nuclei, finely dispersed chromatin, smooth nuclear membrane, and single small nucleoli are typical of RO (Amin et al., 1997; Perez-Ordonez et al., 1997; Tickoo et al., 1997; Kuroda et al., 2003a). Chromophobe RCC is characterized by solid, tubular, cystic, and stone paving-type growth pattern; the presence of large, pale, and small eosinophilic cells; distinct eosinophilic cell borders; and nuclei with irregular or wrinkled contours (Tickoo et al., 1999; Nagashima, 2000; Kuroda et al., 2003b; Brunelli et al., 2005). Composite tumors have at least 20% of the area showing the cytologic and architectural features of either chromophobe RCC or RO (Fig. 2A,B). Hybrid tumor is the intermediate or incomplete form of the diagnostic criteria of chromophobe RCC and RO (Tickoo et al., 1999; Leroy et al., 2001; Chen et al., 2003; Cossu-Rocca et al., 2008; Gobbo et al., 2010). Smaller oncocytic lesions show the histologic features of RO, chromophobe RCC (Fig. 2C), or nodules with hybrid morphology. Infiltrative growth of oncocytic cells, cortical cysts with oncocytic features (Fig. 2D), or extensive oncocytic change in non-neoplastic tubules (Fig. 2C) are also frequently observed (Tickoo et al., 1999; Menendez et al., 2007). In oncocytic “dysplastic (in situ) lesions,” characteristic retraction spaces (windows) may be observed (Huang et al., 2009). In differential diagnosis by core needle biopsy, the risk of misdiagnosis may be high among hybrid tumor, chromophobe RCC, and RO in renal oncocytosis; however, the identification of oncocytic parenchymal lesions may lead to the diagnosis of renal oncocytosis (Campodonico et al., 2002; Huang et al., 2009; Val-Bernal et al., 2011). Myofibroblasts are observed in the stroma of renal oncocytosis, as observed in the stroma of RO (Yen et al., 2010).

Histochemical findings

Hybrid tumor cells show weak focal positivity for Hale’s colloidal iron, whereas chromophobe RCCs show a strong cytoplasmic reaction with this stain (Gobbo et al., 2010). However, some reports indicate that chromophobe cells in hybrid tumors show diffuse cytoplasmic staining for Hale’s colloidal iron (Leroy et
A positive reaction to this stain in RO is limited to the apical lumen (Leroy et al., 2001; Mazzucchelli et al., 2008).

**Immunohistochemical findings**

Neoplastic cells of hybrid tumors demonstrate strong parvalbumin immunoreactivity, but variable cytokeratin 7 and S100A1 immunoreactivity (Gobbo et al., 2010). The immunohistochemistry of CD117 has not been investigated to date. Chromophobe RCCs show diffuse immunoreactivity for cytokeratin 7 and parvalbumin, but negativity for S100A1 (Gobbo et al., 2010). ROs show negativity or focal positivity for cytokeratin 7 and negativity for alpha-methylacyl-CoA racemase (AMACR, P504S) (Chen et al., 2003; Mazzucchelli et al., 2008). Oncocytic nodules show intense reactivity with anti-mitochondrial antigen (Nagashima et al., 2005).

**Ultrastructural findings**

In one published case of hybrid tumor occurring within oncocytsis, the cytoplasm in the RO-like area contained abundant mitochondria with lamellar cristae, whereas the cytoplasm in the chromophobe RCC-like area showed a significantly reduced number of mitochondria with lamellar cristae, an increased amount of glycogen, and no evident cytoplasmic microvesicles (Chen et al., 2003). In one unclassified oncocytic tumor occurring as part of oncocytsis, neoplastic cells contained numerous mitochondria of small and uniform

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Fig. 2. Microscopic findings. A. Low-power magnification view of composite tumor showing a mixture of pale and oncocytic cells. B. High-power magnification view of composite tumor. Nuclei of pale and oncocytic cells resemble those of regular chromophobe RCC and oncocytoma, respectively. The perinuclear halo characteristic of chromophobe RCC is absent. C. Two small chromophobe RCC-like lesions surrounding an oncocytic tubule. D. Cyst lining with oncocytic change. A, x 100; B, x 200; C, D, x 40
size, but no microvesicles were observed (Nagashima et al., 2005).

Differential diagnosis

With regard to differential diagnosis, pathologists must consider BHD syndrome and sporadic hybrid oncocytic/chromophobe tumor (SHOCT). BHD syndrome is characterized by the presence of skin lesions such as fibrofolliculoma or trichodiscoma on the face or head and neck, bullae with spontaneous pneumothorax, and multiple renal tumors; family history is also very relevant (Pavlovich et al., 2002; Adley et al., 2006; Furuya et al., 2012). Renal lesions in BHD syndrome may demonstrate hybrid tumor, chromophobe RCC, or RO, in association with several renal oncocytic parenchymal lesions (Pavlovich et al., 2002; Adley et al., 2006; Nagashima et al., 2012). Hybrid tumor in BHD syndrome may often contain clear cells (Adley et al., 2006). SHOCT can occur sporadically, presenting as a solitary mass (Delongchamps et al., 2009; Petersson et al., 2010). In this condition, tumor cells display a solid alveolar architecture and oncocytic cytoplasm with focally present perinuclear halos. Binucleated cells are occasionally observed, but hyperchromatic or wrinkled nuclei and irregular nuclear margins are absent (Petersson et al., 2010).

Cytogenetic and molecular genetic findings

A gain of chromosomes 1, 2, 6, 10, and 17 was identified in three hybrid tumors, and a gain of chromosomes 1 and 17 was identified in one hybrid tumor (Gobbo et al., 2010). Additionally, in two studies many hybrid tumors showed a disomic status for chromosomes 1, 2, 6, 10, or 17 (Cossu-Rocca et al., 2008; Gobbo et al., 2010). In G-banding of one pediatric hybrid tumor, a probable deletion of del(20)(p11.22) was identified in 2 of 20 metaphase spreads (Chen et al., 2003). In chromophobe RCC, loss of chromosomes 1, 6, 10, and 17 was repeatedly observed (Gobbo et al., 2010). In FISH analyses, many ROs showed disomy for chromosomes 1, 2, 6, 10, or 17; however, the loss of chromosome 1 was seen in three cases of RO (Mazzucchelli et al., 2008; Cossu-Rocca et al., 2008; Gobbo et al., 2010). Al-Saleem et al. (2004), using microsatellite analysis, reported a case of renal oncocytosis with renal oncocytoma showing normal karyotype and hybrid tumor with the loss of chromosomes 1, 14, 21, and Y and the loss of heterozygosity for chromosomes 1p, 14q, and 21q. These authors suggested that hybrid tumors may represent a possible model of progression from RO to chromophobe RCC. However, their results appear to be inconsistent with those of Cossu-Rocca et al. (2008) or Gobbo et al. (2010). One possible explanation is that different methodologies were used for the detection of chromosomal abnormalities. Germ line mutation of the folliculin gene, which is responsible for oncogenesis in BHD syndrome, was not observed in one unclassified oncocytic tumor (Nagashima et al., 2005). A concordant pattern of nonrandom X-chromosome inactivation in coexisting multiple tumors was identified in one case of renal oncocytosis with hybrid morphology (Gobbo et al., 2010).

Therapy

Because patients with renal oncocytosis usually present with multiple and bilateral renal nodules, partial nephrectomy is one possible approach. Careful surveillance of the remaining renal masses should be carried out subsequently (Adamy et al., 2011).

Prognosis

The prognosis of this multitumor condition is generally favorable and tumors seldom follow an aggressive clinical course (Mazzucchelli et al., 2008; Ariaratnam et al., 2008; Adamy et al., 2011).

Future perspectives

The hybrid tumor arising in sporadic-type renal oncocytosis, with chronic renal failure/long-term hemodialysis, seems to be genetically distinct from “sporadic” chromophobe RCC or RO. It is unlikely that such tumors represent an intermediate form between chromophobe RCC and RO cytogenetically because chromosomal changes in hybrid tumors are not identical to those of chromophobe RCC or RO. A gain of chromosomes 1, 2, 6, 10, and 17, as identified in some hybrid tumors, has not been found in chromophobe RCC or RO (Cossu-Rocca et al., 2008; Gobbo et al., 2010). However, it is likely that the hybrid tumor of renal oncocytosis is derived from progenitor cells common to both chromophobe RCC and RO, namely intercalated cells of the collecting duct (Tickoo et al., 1999; Leroy et al., 2004). The gene responsible for the occurrence of renal oncocytosis remains unknown, but appears to be distinct from that associated with BHD syndrome (Nagashima et al., 2005). Some multifocal and bilateral ROs with chromophobe RCC-like areas, or some multifocal and bilateral chromophobe RCCs with RO-like areas that have been previously reported, may currently be categorized within the entity of renal oncocytosis (Amin et al., 2008; Trpkov et al., 2010). Further examination involving a large-scale study is required to elucidate the pathogenesis of renal oncocytosis.

References


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