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Review

Review of renal oncocytoma with focus on clinical and pathobiological aspects

N. Kuroda[1], M. Toi[1], M. Hiroi[1], T. Shuin[2] and H. Enzan[1]

[1]First Department of Pathology and [2]Department of Urology, Kochi Medical School, Kohasu, Oko-cho, Nankoku City, Kochi, Japan

Summary. Renal oncocytomas account for about 3-7% of all renal tumors. Macroscopically, the cut surface of the tumor is generally mahogany brown or dark red in color. A central scar is occasionally observed. Histologically, tumor cells with finely granular cytoplasm proliferate in an edematous, myxomatous or hyalinized stroma with a nested, tubulocystic, solid or trabecular pattern. Ultrastructurally, tumor cells contain many mitochondria with lamellar cristae. Mitochondrial DNA alterations are consistently observed in renal oncocytomas. In chromosomal analysis, renal oncocytomas comprise a heterogenous group. Combined loss of chromosomes Y and 1, rearrangements affecting band 11q12-13, involvement of 12q12-13, loss of 14q, and the lack of combination of LOH at specific chromosomal sites have been reported. In differential diagnosis, the histological separation from chromophobe RCCs is of great importance. In such a setting, ultrastructural or chromosomal analysis is very useful. However, there are several findings suggesting a close relationship between chromophobe RCC and oncocytoma. First, both tumors share a phenotype of intercalated cells of the collecting duct system and mitochondrial DNA alterations. Second, some cases of coexistent oncocytoma and chromophobe RCC, designated as "renal oncocytosis", have recently been reported. Third, oncocytic variants of chromophobe RCCs that have similar ultrastructural features to those of oncocytomas have been reported. Fourth, the existence of chromophobe adenoma, which is the benign counterpart of chromophobe RCC and shows loss of chromosomes Y and 1, has recently been suggested. Finally, although almost all oncocytomas behave in a benign fashion, some cases of oncocytoma that caused metastasis or resulted in death have also been reported. Therefore, further studies are needed to resolve these problems and also to elucidate the genetic mechanisms responsible for the occurrence of oncocytomas.

Key words: Renal oncocytomas, Pathology, Chromosomal abnormalities

Offprint requests to: Dr. Naoto Kuroda, First Department of Pathology, Kochi Medical School Kohasu, Oko-cho, Nankoku City, Kochi 783-8505, Japan. Fax: +81-88-880-2332. e-mail: nkuroda@kochi-ms.ac.jp

History of the establishment of the disease concept

The first case of renal oncocytoma was reported by Zippel in 1942. Since then, some individual cases have been described in the European literature. In 1976, Klein and Valeni reported 13 cases of renal oncocytoma. Since their report, the concept of this tumor has become widely accepted. Although these tumors have been designated as proximal tubular adenomas with so-called oncocytic features, many investigators have suggested that these tumors originate from intercalated cells of the collecting duct system, and the term "oncocytoma" is generally accepted at present (Ortmann et al., 1988a,b; Störkel et al., 1988; Lyzak et al., 1994). Kovacs et al. (1989) confirmed that renal oncocytoma is a distinct entity in both genotypic and phenotypic aspects . In recent classifications, oncocytoma has also been regarded as a separate entity (Kovacs et al., 1997; Störkel et al., 1997). Renal oncocytomas account for aproximately 3-7% of all renal tumors (Akhtar and Kott, 1979; Mei et al., 1980; Lieber et al., 1981; Merino and Livolsi, 1982; Choi et al., 1983; Alanen et al., 1984; Morra and Das, 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997).

Clinical symptoms and signs

More than 50% of patients with oncocytomas are asymptomatic (Mei et al., 1980; Lieber et al., 1981; Merino and Livolsi, 1982; Choi et al., 1983; Licht et al., 1993; Morra and Das, 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997). Flank pain, a palpable mass, gross or microscopic hematuria, or weight loss is seen in some patients (Mei et al., 1980; Lieber et al., 1981; Merino and Livolsi, 1982; Choi et al., 1983; Alanen et al., 1984; Licht et al., 1993; Amin et al., 1997; Perez-Ordoñez et

al., 1997).

Other clinical features

Bilateral or multifocal oncocytomas are sometimes seen (Fairchild et al., 1983; Hunt et al., 1983; van den Walt et al., 1983; Licht et al., 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997; Dechet et al., 1999). The coexistence of oncocytoma and renal cell carcinoma has also been reported (Kavoussi et al., 1985; Licht et al., 1993; Dechet et al., 1999). An association with angiomyolipoma or tuberculous sclerosis in some patients has been reported (Srinivas et al., 1985; Talic et al., 1996). The occurrence of oncocytoma in transplant patients has also been reported (Rostaing et al., 1994). Familial cases of oncocytoma have also been found (Weirich et al, 1998).

Radiological findings

Ultrasound sonography or computed tomography (CT) scan of the tumor generally shows a solid mass, but some oncocytomas are identified as partially cystic lesions (Mei et al., 1980; Morra and Das, 1993). Findings suggestive of oncocytoma in magnetic resonance imaging (MRI) are a low-intensity homogenous mass on T1-weighted images, which appears as increased intensity on T2-weighted images, the presence of a capsule, central scar or satellate pattern and the absence of either hemorrhage or necrosis (Ambos et al., 1978). Intravenous pyelography (IVP) shows a mass defect (Mei et al., 1980; Choi et al., 1983). Renal angiography of many oncocytomas shows hypervascularity (Merino and Livolsi, 1982; Morra and Das, 1993). Typically, the vascularity displays a spoked-wheel pattern (Alanen et al., 1984; Morra and Das, 1993; Harmon et al., 1996).

Pathological findings

Macroscopic findings

Renal oncocytomas are typically well-circumscribed and often encapsulated (Akhtar and Kott, 1979; Merino and Livolsi, 1982; Choi et al., 1983; Morra and Das, 1993). The color of the cut surface is mahogany brown to dark red (Akhtar and Kott, 1979; Mei et al., 1980; Merino and Livolsi, 1982; Choi et al., 1983; Morra and Das, 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997). The mean tumor size and range of sizes were reported by Amin et al. (1997) to be 4.4 cm and 0.6-15 cm, respectively, and were reported by Perez-Ordoñez et al. (1997) to be 5.0 cm and 1.5-14 cm, respectively. Necrosis and hemorrhage are uncommon, but hemorrhagic foci may be present in larger tumors (Mei et al., 1980; Merino and Livolsi, 1982; Choi et al., 1983; Morra and Das, 1993; Amin et al., 1997). A central white-colored scar is occasionaly observed, especially in larger tumors (Mei et al., 1980; Choi et al., 1983; Amin et al., 1997; Perez-Ordoñez et al., 1997). Extensive cystic change is very rare (Ogden et al., 1987).

Microscopic findings

Histologically, oncocytomas consist of round-to polygonal-shaped cells with an abundant finely granular cytoplasm (Akhtar and Kott, 1979; Mei et al., 1980; Choi et al., 1983; Alanen et al., 1984; Morra and Das, 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997). The following various growth patterns are observed:

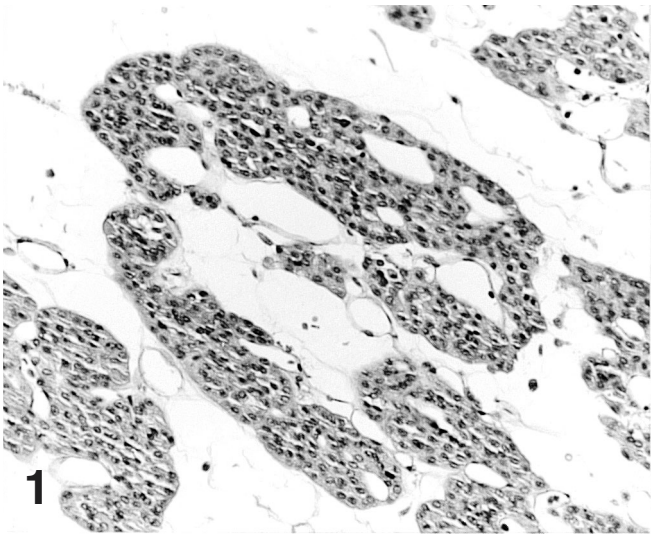

Fig. 1. Tumor cells with granular cytoplasm proliferate with a nesting formation in the edematous stroma. x 25

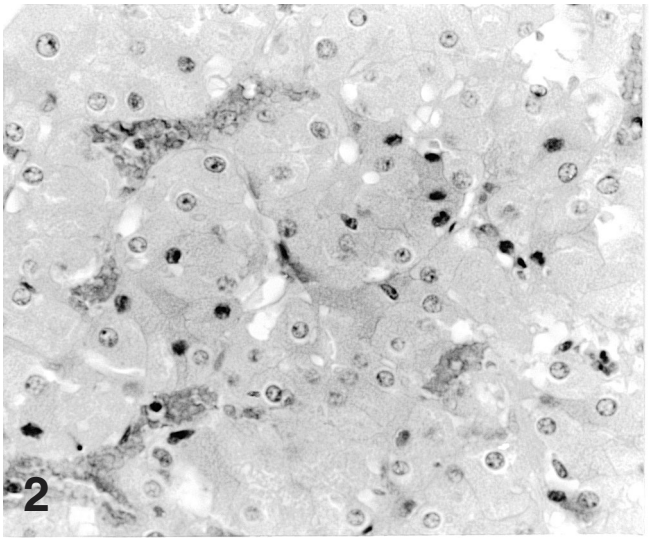

Fig. 2. The nuclei are centrally located and round. Cells borders are indistinct. x 50

compact nesting (Fig. 1) and acini, and solid, microtubular or microcystic, trabecular and small papillae (Akhtar and Kott, 1979; Merino and Livolsi, 1982; Choi et al., 1983; Alanen et al., 1984; Morra and Das, 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997). A prominent papillary architecture is uncommon (Amin et al., 1997). A loose edematous and myxoid or hyalinized stroma is chracteristic (Fig. 1) (Choi et al., 1983; Amin et al., 1997; Perez-Ordoñez et al., 1997). The nucleus is homogenous, round and centrally located (Fig. 2) (Mei et al., 1980; Amin et al., 1997; Perez-Ordoñez et al., 1997). Nuclear atypia or pleomorphism is frequenty seen (Akhtar and Kott, 1979; Merino and Livolsi, 1982; Choi et al., 1983; Amin et al., 1997; Perez-Ordoñez et al., 1997). Binucleation is present but infrequent (Alanen et al., 1984; Amin et al., 1997; Perez-Ordoñez et al., 1997). Foci of cytoplasmic clearing in the region of scarring or intracytoplasmic vacuoles are rarely seen (Slagel and Bonsib, 1995; Perez-Ordoñez et al., 1997; Koller et al., 2000). Cells with scant cytoplasm and large nuclei, namely "oncoblasts", may sometimes be present (Perez-Ordoñez et al., 1997). An extension into adjacent renal parenchyma or perinephric fat is sometimes observed (Lieber et al., 1981; Alanen et al., 1984; Amin et al., 1997; Perez-Ordoñez et al., 1997). Vascular invasion is also rarely seen (Lieber et al., 1981; Perez-Ordoñez et al., 1997). Mitotic activity is also sometimes observed, but abnormal mitotic figures are never seen (Merino and Livolsi, 1982; Choi et al., 1983; Amin et al., 1997; Perez-Ordoñez et al., 1997).

Histochemical and immunohistochemical findings

Although earlier stuides showed that most oncocytomas are negative for Hale's colloidal iron, recent studies have shown that apical lumens of oncocytomas are occasionally positive for this staining. However, this reaction is weak and focal (Cochnd-Priollet et al., 1997; Tickoo et al., 1998; Skinnider and Jones, 1999). In lectin histochemistry, some oncocytomas show positive reaction for *Dolichos biflorus* (DBA) and *Glycine max* (SBA), while others are positive for *Lotus tetragonolobus* (LTA) (Eble and Hull, 1988; Lyzak et al., 1994; Ortmann et al., 1998a). Holthöfer (1987) reported that *Triticum vulgaris* (wheat germ agglutinin; WGA) and Concanavalin A (Con A) are useful markers for the detection of oncocytomas. Immunohistochemically, oncocytomas are generally positive for epithelial membrane antigen (EMA), erythrocyte anion exchanger band 3, and carbonic anhydrase C and negative for vimentin (Pitz et al., 1987; Ortmann et al., 1988a,b; Störkel et al., 1988; Lyzak et al., 1994). Cytokekeratins 14 and 20 are also positive for the cytoplasm of oncocytomas (Chu and Weiss, 2001; Stopyra et al., 2001). Kuroda et al. (2000 and 2001) reported that vinculin and paxillin, which play roles in the focal adhesion between cells and matrix, are useful markers for renal neoplasms with a collecting duct

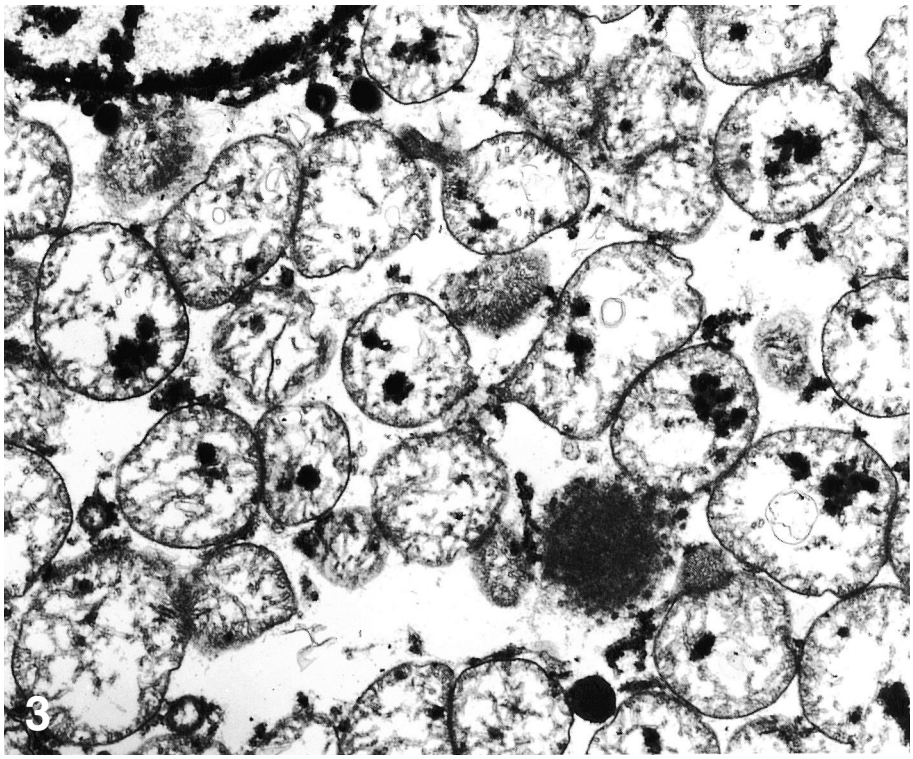

Fig. 3. Ultrastructural findings of an oncocytoma cell. Tumor cells contain many mitochondria. x 6,000

phenotype, including oncocytomas and chromophobe RCCs.

Ultrastructural findings

The cytoplasm of tumor cells is generally filled with mitochondria, and other organellae are scant (Fig. 3) (Mei et al., 1980; Merino and Livolsi, 1982; Choi et al., 1983; Fairchild et al., 1983; Krizanac et al., 1987; Perez-Ordoñez et al., 1997). Occasionally, the Golgi apparatus and free ribosomes are evident. Fat vacuoles are absent (Mei et al., 1980; Merino and Livolsi, 1982). The mitochondria are predominantly uniform and round with predominantly lamellar cristae (Erlandson et al., 1997; Perez-Ordoñez et al., 1997; Tickoo et al., 2000). Cytokeratin-containing globular filamentous bodies are frequently seen in the tumor cytoplasm (Bonsib and Bray, 1991; Stopyra et al., 2001). Microvilli and attentuated desmosomes are present, but brush borders are absent (Mei et al., 1980; Lieber et al., 1981).

Cytological findings

In aspiration smears, numerous tubular cells are observed. These cells are characterized by abundant granular cytoplasm with frayed borders and monotonous, small, dark nuclei. Additionally, a small cluster of much larger cells is also seen. These cells possess abundant granular cytoplasm with large nuclei (Rodriguez et al., 1980).

Flow cytometric analysis

Ploidy analysis of oncocytomas generally reveals a diploid pattern and rarely near-diploid aneuploidy (Eble and Sledge, 1986; Hartwick et al., 1992; Licht et al., 1993). Rainwater et al. (1986), however, reported that oncocytomas commonly have polyploid and aneuploid DNA histograms. However, some of the oncocytomas examined in their study seem to have been chromophobe RCCs.

Mitochondrial DNA alterations

Kovacs et al. (1989) and Walter et al. (1989) reported that mitochondrial DNA shows an abnormal restriction fragment pattern in all oncocytomas. Kovacs therefore regards renal oncocytoma as a mitochondrial disease. Tallini et al. (1994), on the other hand, reported that no mitochondrial DNA alterations were found in oncocytomas.

Chromosomal Analyses (karyotyping, fluorescence in situ hybridization (FISH), Southern blot, comparative genomic hybridizazion (CGH), restriction fragment length pleomorphism (RELP), microsatellite analysis)

In karyotyping, three representative abnormalities have been reported: combined loss of sex (Y or X, predominantly Y) chromosome and chromosome 1; rearrangements affecting band 11q12-13; and involvement of 12q12-13 (Miles et al., 1988; Psihramis et al., 1988; Walter et al., 1989; Crotty et al., 1992; Meloni et al., 1992; Füzesi et al., 1994, 1998; van den Berg et al., 1995; Dal Cin et al., 1996, 1999; Neuhaus et al., 1997; Feder et al., 2000). Kovacs et al. (1987b, 1989) reported a mosaic chromosomal pattern of cells with normal and abnormal clones. Balzarini et al. (1999) also reported groups of renal oncocytomas with heterogenous and atypical chromosomal changes. Dobin et al. (1992) reported monosony of chromosome 22 and trisomy of chromosome 12 as well as abnormalities of a sex chromosome and chromosome 1. However, one of the five tumors examined in their study seems to have been a chromophobe RCC. Dal Cin et al. (2000) reported a case of combination of loss of 1p and monosomy 18. Kovacs et al. (1987a,b) described a telomeric association in oncocytomas. Brown et al. (1996) reported that results of FISH analysis showed a combined loss of chromosomes Y and 1 in five male cases and a loss of chromosome 1 in two female cases. Sinke et al. (1997) have reported that the results of FISH and Southern blot analyses suggest that the breakpoint in chromosome band 11q13 is located within a genomic interval of at maximum 400 kb immediately centromeric to the BCL1 locus. In a recent study using both karyotyping and FISH analysis, Leroy et al. (2002) found a renal oncocytoma with a novel chromosomal rearrangement, der(13)t(13;16)(p11;p11), associated with a conventional RCC. In CGH analysis, loss of chromosomes 1 and/or 14 is occasionally found (Presti et al., 1996). RELP analysis has revealed LOH at the 3p21 telomeric locus in one out of seven oncocytomas. However, it has been shown that chromosome 3 is not involved in oncocytomas (Kovacs et al., 1989; Brauch et al., 1990; El-Naggar et al., 1993). Using microsatellite analysis, Herbers et al. (1998) found that oncocytomas can be differentiated from other RCCs by a lack of combination of LOH at specific chromosomal sites. Thrash-Bingham et al. (1996) reported that LOH of chromosome arm 1p frequently occcurs in oncocytomas. Schwerdtle et al. (1997) reported that LOH frequently occurs at 14q23-24.3 and 14q32.1-32.2.

In summary, renal oncocytomas compose a genotypically heterogenous group. However, many oncocytomas show a normal karyotype (Kovacs et al., 1997).

Differential diagnosis in histopathology

Differentiation between chromophobe RCCs, conventional RCCs with granular cytoplasm, papillary RCCs and angiomyolipoma is necessary (Licht et al., 1993; Perez-Ordóñez et al., 1997). Among them, differentiation from chromophobe RCCs is the most important for diagnosis (Licht et al., 1993; Perez-Ordoñez et al., 1997; Tickoo et al., 1997, 2000; Tickoo

and Amin, 1998; Tickoo, 2000). Macroscopically, oncocytomas are generally mahogany brown or dark red in color, whereas chromophobe RCCs are beige (Licht et al., 1993; Perez-Ordoñez et al., 1997; Tickoo et al., 1997, 2000; Tickoo and Amin, 1998; Tickoo, 2000). Conventional RCCs show a yellow color and papillary RCCs show a yellow or brown color (Tickoo et al., 1997; Tickoo, 2000). Microscopically, oncocytomas are composed of epithelial cells with abundant homogenously and finely granular cytoplasm (Akhtar and Kott, 1979; Merino and Livolsi, 1982; Choi et al., 1983; Alanen et al., 1984; Morra and Das, 1993; Amin et al., 1997; Perez-Ordoñez et al., 1997). The nucleus is centrally located and more rounded in oncocytomas than in RCCs (Castren et al., 1995; Perez-Ordoñez et al., 1997; Tickoo, 2000). A perinuclear halo tends to appear in chromophobe RCCs (Perez-Ordoñez et al., 1997; Tickoo et al., 1997; Tickoo and Amin, 1998; Tickoo, 2000). In contrast to those in chromophobe RCCs, cell borders in oncocytomas are indistinct (Tickoo et al., 2000). If the papillary projection is prominent, the tumor is unlikely to be an oncocytoma (Amin et al., 1997; Tickoo et al., 1997). Histochemically, Hale's colloidal iron shows a diffuse and strong positive staining pattern in chromophobe RCCs but usually a focal and weak staining pattern in oncocytomas or other RCCs (Amin et al., 1997; Cochand-Priollet et al., 1997; Tickoo et al., 1998; Skinnider and Jones, 1999).

Immunohistochemically, vimentin is positive for conventional RCCs but negative for oncocytomas or chromophobe RCCs (Pitz et al., 1987; Amin et al., 1997). Angiomyolipomas are generally positive for HMB45.

Chromosomal analysis is more useful. Conventional RCCs have a loss of the 3p segment, and papillary RCCs are characterized by trisomy of chromosomes 16, 12 or 20 in addition to trisomy of chromosomes 7 and 17 and by loss of the Y chromosome (Kovacs et al., 1988, 1991, 1997; Kovacs, 1989, 1990, 1993a,b; Kovacs and Frisch, 1989; Kovacs and Kung, 1991). Furthermore, chromophobe RCCs show a low chromosome number (Kovacs et al., 1988b, 1997; Kovacs and Kovacs, 1992). However, these characteristic abnormalities are never seen in renal oncocytomas (Herbers et al., 1998).

Treatment and prognosis

Most patients with oncocytomas are treated with radical nephrectomy. Partial nephrectomy, enucleation or wegde resection may be performed (Morra and Das, 1993; Perez-Ordoñez et al., 1997). Almost all cases of oncocytoma behave in a benign fashion with no recurrence, metastasis or mortality (Akhtar and Kott, 1979; Mei et al., 1980; Merino and Livolsi, 1982; Choi et al., 1983; Alanen et al., 1984; Amin et al., 1997; Perez-Ordoñez et al., 1997). Some atypical features, such as nuclear pleomorphism, perinephric fat involvement and focal necrosis, do not influence the prognosis of patients with oncocytomas (Akhtar and Kott, 1979; Alanen et al., 1984; Amin et al., 1997).

Conclusions and perspectives

Renal oncocytoma can be regarded as a distinct entity in both clinicopathological and genetic aspects. Some malignant oncocytomas have been described in early reports (Lieber et al., 1981; Morra and Das, 1993). However, the new entity of chromophobe RCCs was established (Thoenes et al., 1985; Störkel et al., 1989). These RCCs and oncocytomas sometimes show overlapping histological features (Licht et al., 1993; Perez-Ordoñez et al., 1997; Schwerdtle et al., 1997; Tickoo et al., 1997, 2000; Tickoo and Amin, 1998). Therefore, many of the previously reported maligant oncocytomas could be categorized into eosinophilic or oncocytic variants of chromophobe RCC. However, despite the strict histological criteria, oncocytomas that caused metastasis or death have recently been reported (Perez-Ordoñez et al., 1997). Chromosomal analysis is needed to determine whether those oncocytomas were actually malignant. Additionally, there are some findings suggeting a close association between these chromophobe RCC and oncocytoma tumors. Chromophobe RCCs as well as oncocytomas show mitochondrial DNA alterations (Kovacs et al., 1992). Some cases of coexistent oncocytoma and chromophobe RCC, designated as "renal oncocytosis", have also been reported recently (Tickoo et al., 1999). On the other hand, van den Berg et al. (1997) and Dijkhuizen et al. (1997) consider that oncocytomas with loss of chromosomes 1 and Y can be categorized as chromopobe adenomas. Further studies are needed to elucidate the relationship between oncocytomas and chromophobe RCCs and to identify the key gene that gives rise to oncocytomas.

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