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Review

Review of chromophobe renal cell carcinoma with focus on clinical and pathobiological aspects

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Summary. In recent years, the concept of chromophobe renal cell carcinoma (RCC) has been established. Chromophobe RCCs account for about 4-6% of all renal tumors. Macroscopically, the cut surface of the tumor is generally grey-beige in color. Histologically, there are two variants (typical and eosinophilic). In the typical variant, large tumor cells with architecture of a compact tubulo-cystic pattern proliferate. The cytoplasm is abundant and shows a fine reticular translucent pattern. The cell border is thick, prominent and eosinophilic. In the eosinophilic variant, tumor cells are smaller and markedly eosinophilic, and a perinuclear halo is often seen. Histochemically, the tumor cells generally show a diffuse and strong reaction for Hale's colloidal iron staining. Ultrastructurally, tumor cells contain many cytoplasmic microvesicles (150-300 nm). In chromosomal analysis, a low chromosome number is characteristic of chromophobe RCCs, due to the frequent occurrence of a combined loss of chromosomes 1, 2, 6, 10, 13, 17, and 21. In differential diagnosis, histological distinction from oncocytomas, which share a common phenotype (intercalated cells of the collecting duct system), is most important. In this diagnostic setting, recent studies have given rise to several problems. Firstly, some cases of coexistent chromophobe RCC and oncocytoma (so-called renal oncocytosis) or cases of oncocytoma with metastasis have recently been reported. Secondly, the existence of chromophobe adenoma, which is the benign counterpart of chromophobe RCC, and an oncocytic variant of chromophobe RCC has recently been suggested. Therefore, further studies are needed to elucidate the relationship between chromophobe RCCs and oncocytomas, to confirm whether chromophobe adenoma actually exists or not, and to identify the key gene that causes chromophobe RCCs.

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History of the establishment of the disease concept

Bannasch et al. (1974) described "chromophobe adenoma" as a rare form of renal tumor that was experimentally induced by injection of nitrosomorpholine. Thoenes et al. (1985) found that this form is also present in human renal tumors, and they named it "chromophobe cell renal carcinoma". They later added this subtype to the classification of renal tumors (Thoenes et al., 1986).

Some investigators consider that this tumor is derived from intercalated cells of the cortical collecting duct system (Störkel et al., 1989; Ortmann et al., 1991; Durham et al., 1996). Before the establishment of this disease concept, chromophobe renal cell carcinomas (RCCs) were probably classified into conventional RCCs (previously clear and granular cell carcinomas) or oncocytomas. Therefore, many previously reported cases of malignant oncocytoma may actually be chromophobe RCCs (Nagashima, 2000).

Epidemiology

Chromophobe RCCs account for about 4-6% of all renal tumors (Thoenes et al., 1988). The mean age and range of ages of patients in a series of 50 patients reported by Crotty et al. (1995) were 53 years and 30-83 years, respectively. There is no tendency of sex predominance (Akhtar et al., 1995; Crotty et al., 1995).

Clinical symptoms and signs

Flank discomfort or pain, gross hematuria, flank mass, and weight loss are observed as symptoms (Fukushima et al., 1994; Akhtar et al., 1995; Crotty et al., 1995). Patients with classical triads, namely hematuria, flank discomfort and an abdominal mass, are

rare (Crotty et al., 1995). Some tumors are incidentally discovered during evaluation of other problems (Akhtar et al., 1995; Crotty et al., 1995).

Radiological findings

Radiographically, most chromophobe RCCs are revealed solitary and solid masses. Cystic formation or necrosis is seen in less than 10% of tumors by ultrasonography (Crotty et al., 1995). In computerized tomography (CT) scans, tumors are shown as hypodense masses (Akhtar et al., 1995). Renal angiography of chromophobe RCCs generally reveals hypovascularity, but some cases may display significant vascularity (Fukushima et al., 1994; Crotty et al., 1995; Nagashima, 2000).

Pathological Findings

Macroscopic findings

The cut surface of the tumor is generally grey-beige in color (Thoenes et al., 1986, 1988; Akhtar et al., 1995; Durham et al., 1996; Nagashima, 2000). The mean size and range of sizes of tumors in a large series studied by Crotty et al. (1995) were 8.5cm and 2.5-22cm, respectively. Hemorrhage or necrosis may sometimes be present (Bonshib and Lager, 1990; Akhtar et al., 1995; Crotty et al., 1995). Irregular fibrosis is common (Crotty et al., 1995). Tumors are generally well-circumscribed and frequently have a fibrous capsule, particularly in the early stage (Crotty et al., 1995).

Microscopic findings

Thoenes et al. (1985, 1988) have described two variants, typical (light) and eosinophilic variants. The presence of an oncocytic variant has been reported by Erlandson et al. (1997) and has also been confirmed by Latham et al. (1999). In the typical variant, proliferation of various-sized voluminous tumor cells arranged in large sheets separated by fibrovascular septa is seen. A tubuloalveolar or cystic pattern is also observed. The cytoplasm is abundant and shows a fine reticular translucent pattern. The cell border is thick, prominent and eosinophilic (Thoenes et al., 1985, 1986, 1988). In the eosinophilic variant, tumor cells are smaller and markedly eosinophilic, the cytoplasm is finely granular, and a perinuclear halo is often seen (Thoenes et al., 1986, 1988; Crotty et al., 1995). Microscopic findings of an oncocytic variant have not been fully described in the literature, but it is possible that the histological findings of this variant are similar to those of oncocytoma. Therefore, it may be difficult to distinguish oncocytic variant of chromophobe RCC from oncocytoma at the level of electron microscopy (Erlandson et al., 1997; Latham et al., 1999).

Histochemical and immunohistochemical findings

The tumor cells generally stain positively for Hale's colloidal iron and stain weakly with alcian blue (Thoenes et al., 1985, 1986, 1988). The content of glycogen in the tumor cytoplasm is lower than that in conventional (clear) RCCs (Thoenes et al., 1986). Earlier studies suggested that positivity for Hale's colloidal iron stain occurr exclusively in chromophobe RCCs (Thoenes et al., 1986, 1988). However, recent studies have shown that other renal tumors, including clear RCCs, papillary RCCs and oncocytomas, also display positive reactions for Hale's colloidal iron stain with various distributions and intensities (DeLong et al., 1996; Cochnad-Priollet et

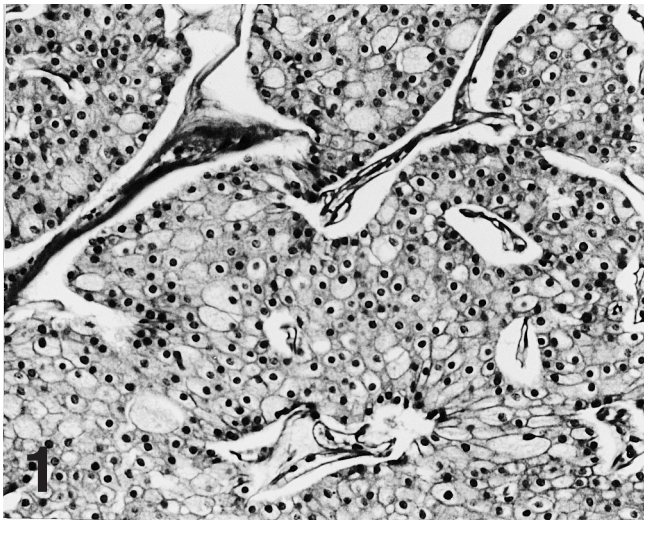

Fig. 1. Histological features of a typical variant of chromophobe RCC. Proliferation of various-sized voluminous tumor cells arranged in large sheets separated by fibrovascular septa can be seen. x 25

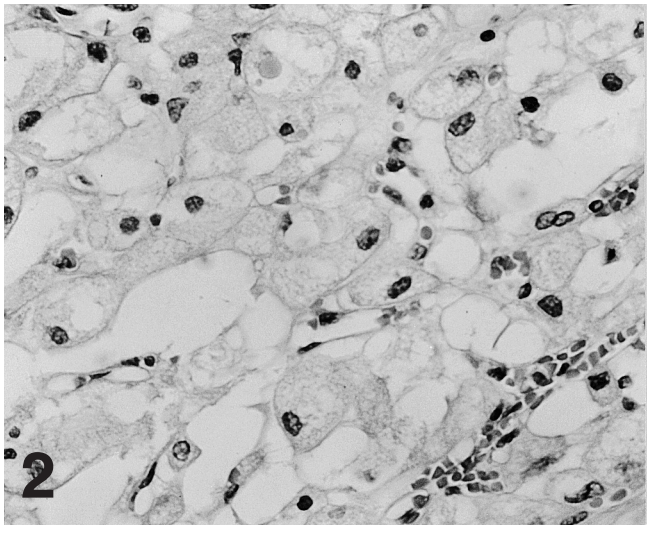

Fig. 2. The cytoplasm is abundant and shows a fine reticular pattern. The cell border is thick, prominent and eosinophilic. The nuclei are generally wrinkled, and binucleated cells are occasionally seen. x 100

al., 1997; Tickoo et al., 1998; Skinnider and Jones, 1999; Tickoo, 2000). Therefore, we should consider that diffuse and strong reticular positivity for colloidal iron stain is significant for the diagnosis of chromophobe RCCs (Tickoo et al., 1998; Skinnider and Jones, 1999; Tickoo, 2000). Tickoo et al. (1998) reported that the modified Mowry's method (treatment of sections with 3% acetic acid before addition of the colloidal iron) gives technically superior staining results than the original method does. The positive reaction for colloidal iron is due to the accumulation of mucopolysaccharide in the tumor cytoplasm (Bonsib et al., 1993). In lectin histochemical study, tumor cells are generally stained by peanut agglutinin (PNA) and *Dolichos biflorus* agglutinin (DBA) (Ortmann et al., 1991). Immunohistochemical stains demonstrate positive reactivity for cytokeratins (No. 8, 18, 19) and epithelial membrane antigen (EMA) and negative reaction for vimentin (Thoenes et al., 1985, 1986, 1988). The authors have found that the immunohistochemical positive rates for SHP2, vinculin, paxillin, osteopontin and CD9 are higher in chromophobe RCCs than in conventional RCCs (Kuroda et al., 1998b, 2000a, 2000b, 2001a, 2001b). Taki et al. (1999) showed that chromophobe RCCs are generally positive for E-cadherin but not N-cadherin.

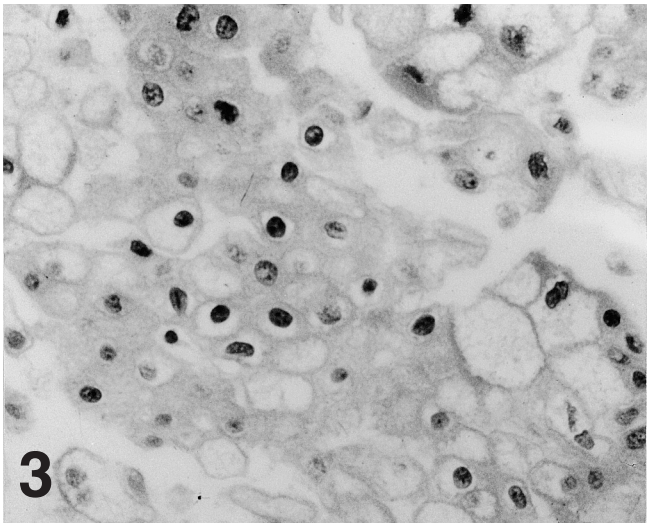

Fig. 3. Perinuclear halos are observed in an esophinophilic variant of chromophobe RCC. x 100

Ultrastructural findings

Ultrastructurally, tumor cells contain many cytoplasmic microvesicles (150-300 nm) (Thoenes et al., 1985, 1986, 1988). In earlier studies, these microvesicles were considered to be a characteristic of this subtype (Thoenes et al., 1986). However, renal tumors such as oncocytomas or eosinophilic variants of conventional RCCs also have some microvesicles in the tumor cytoplasm (Tickoo et al., 2000). Thus, a large number of cytoplasmic microvesicles might be significant for the diagnosis of chromophobe RCCs. Microvesicles are removed by dehydrating agents during paraffin-embedding (Bonsib et al., 1993). Bonsib (1996) suggested that acid mucopolysaccharides are present in microvescles, whereas Billis et al. (1998) suggested that mucopolysaccharides are located outside the microvesicles. Various amounts of mitochondria have also been detected. Generally, mitochodria are present at the peripheral of the tumor cytoplasm and predominantly show tubulo-vesicular cristae (Erlandson et al., 1997; Tickoo et al., 2000). In some cases, electron-dense inclusions may be observed in mitochondria (Erlandson

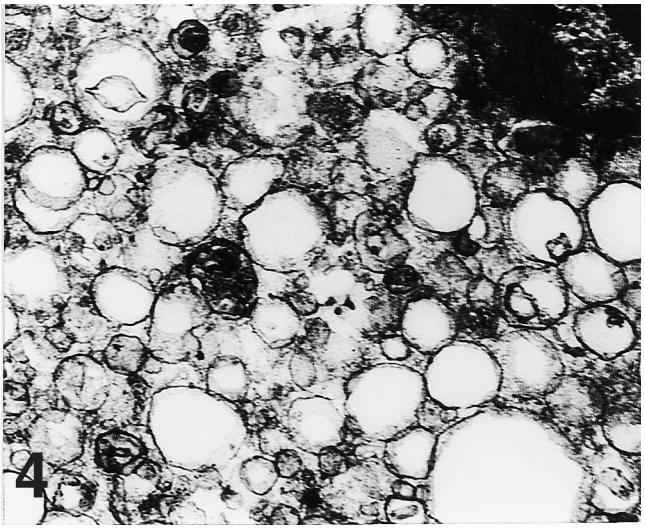

Fig. 4. Ultrastructural findings of a chromophobe cancer cell. The tumor cell contains many cytoplasmic microvesicles. x 40,000

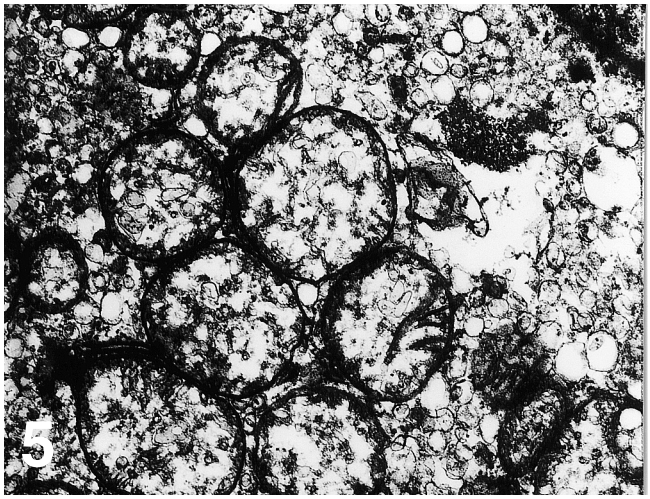

Fig. 5. Ultrastructural findings of a chromophobe cancer cell. Many mitochondria show tubulo-vesicular cristae. x 20,000

et al., 1997). Many investigators have suggested that these microvesicles are derived from mitochondria because of the close relationship between microvesicles and mitochondria at the ultrastructural level, althougth the possibility of endoplasmic reticulum being in the origin has also been suggested (Bannasch et al., 1974; Thoenes et al., 1985, 1986, 1988; Bonsib and Lager, 1990; Tickoo et al., 2000).

Cytological findings

Various cytological findings in samples obtained by fine-needle aspiration have been reported. Akhtar and Ali (1995) emphasized that the presence of three cell types is characteristic of chromophobe RCCs but not of RCCs and oncocytomas. In a typical variant, single cells or small groups of cells tend to be predominant rather than large groups of cells (Renshaw and Granter, 1995; Granter and Renshaw, 1997). Binucleated cells are frequently observed (Renshaw and Granter, 1995; Granter and Renshaw, 1997; Wiatrowska and Zakowski, 1999). The cell border is well-defined and prominent (Akhtar et al., 1996a; Granter and Renshaw, 1997). The cytoplasm is abundant (Akhtar et al., 1996a). The nuclear border is irregular (Akhtar et al., 1996a; Wiatrowska and Zakowski, 1999). In an eosinophilic variant, the granularity of the cytoplasm is not uniform (Akhtar and Ali, 1995; Renshaw and Granter, 1995; Granter and Renshaw, 1997; Wiatrowska and Zakowski, 1999).

Flow cytometric findings

Akhtar et al. (1995, 1996a), and Akhtar and Chanziantoniou (1998) reported that most chromophobe RCCs predominantly impart a hypodiploid nuclear pattern. On the other hand, most conventional RCCs frequently show a diploid nuclear pattern. Bonsib and Lager (1990) found an aneuploid pattern in three out of five cases.

Chromosomal abnormalities (karyotyping, fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), restriction fragment length polymorphism (RELF) and microsatellite analysis)

In karyotyping, Kovacs et al. (1988), and Kovacs and Kovacs (1992a) found that a low chromosome number is a characteristic of chromophobe RCCs. This finding was also confirmed by Shuin et al. (1996), Iqbal et al. (1996) and Gunawan et al. (1999). Loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 frequently occurs in chromophobe RCCs (Kovacs et al., 1988; Kovacs and Kovacs, 1992a; Iqbal et al., 1996; Shuin et al., 1996; Gunawan et al., 1999). Telomeric association is also observed (Kovacs and Kovacs, 1992a; Henn et al., 1993). Iqbal et al. (2000) also found one copy of chromosomes 1, 2, 6, 13, 17, and 21 using the FISH method in touch imprint smear specimens. Furthermore, Spreicher et al. (1994) and Bugert et al. (1997) identified a combination of loss of these chromosomes using CGH and microsatellite analysis, respectively. Schwerdtle et al. (1996) showed, using RELF analysis, that LOHs of chromosomes 1p, 2p, 6p, 10p, 13q, 17p, and 21q are observed with a frequency of 73 to 91%.

Mitochondrial DNA alteration

Kovacs et al. (1992b) found a gross alteration in the restriction pattern of mitochondrial DNA in three chromophobe RCCs.

Differential diagnosis in histopathology

Chromophobe RCCs must be distinguished from conventional RCCs and oncocytomas. The distinction from oncocytomas is most important. Macroscopically, the cut surface of chromophobe RCCs is a beige color (Thoenes et al., 1986, 1988; Akhtar et al., 1995; Durham et al., 1996; Nagashima, 2000). The cut surfaces of conventional RCCs and oncocytomas on the other hand, are yellow and mahogany-brown in color, respectively (Nagashima, 2000; Tickoo, 2000). Typically, oncocytomas have a central scar, but some chromophobe RCCs have a similar fibrosis in the center of the tumor (Crotty et al., 1995; Tickoo, 2000). Microscopically, conventional RCCs have clear cytoplasms and cell borders are not prominent (Thoenes et al., 1986, 1988). Oncocytomas are generally composed of uniform-sized cells with coarse granular cytoplasms and typically show a nesting pattern in an edematous stroma (Nagashima, 2000; Tickoo, 2000). Nuclear features are also important for the disctinction between chromophobe RCCs and oncocytomas. Chromophobe RCCs have wrinkled nuclei, coarse chromatin, and perinuclear halo. Binucleation or multinucleation are also common in chromophobe RCCs. Oncocytomas, on the other hand, have round and uniform-sized nuclei. Nucleoli are more common in oncocytomas (Tickoo and Amin, 1998). Conventional (clear) RCCs are strongly positive for PAS stain because of an abundance of glycogen in the tumor cytoplasm (Thoenes et al., 1986). The staining pattern for antimitochondrial antibody (113-1) may also be useful for distinction among the three types of renal tumor (Tickoo et al., 1997). Immunohistochemically, conventional RCCs are generally reactive for vimentin and CD10 (Thoenes et al., 1986, 1988; Akhtar et al., 1995; Avery et al., 1999). On the other hand, chromophobe RCCs are generally immunoreactive for SHP2, vinculin and paxillin (Kuroda et al., 1998b, 2000a, 2001a). Ultrastructurally, conventional RCCs contain many glycogens and lipid droplets, whereas oncocytomas contain many mitochondria (Thoenes et al., 1986). Mitochondria in oncocytomas typically have lamellar cristae (Erlandson et al., 1997; Tickoo et al., 2000). Chromosomal analysis may also be helpful for distinction (Crotty et al., 1992; Kovacs et al., 1997).

Conventional RCCs have a deletion of chromosome 3p and duplication of chromosome band 5q22. Deletions of chromosome arms 6q, 8p, 9p and 14q are also observed. Oncocytomas show a normal karyotype, loss of chromosome arms 1p and14q and loss of X chromosome or translocation between chromosome arm 11q13 and other chromosomes (Crotty et al., 1992; Kovacs et al., 1997).

Prognosis

Some investigators have suggested that chromophobe RCCs show a more favorable prognosis than conventional RCCs do (Akhtar et al., 1995; Thoenes et al., 1988), whereas others have suggested that the prognosis of chromophobe RCCs is almost identical to that of conventional RCCs (Crotty et al., 1995). Recently, many cases with sarcomatoid transfromation of chromophobe RCCS have been reported (Akhtar et al., 1996b; Aizawa et al., 1997; Gomez-Roman et al., 1997; Hirokawa et al., 1998; Kuroda et al., 1998a; Mai et al., 1999; Wilson et al., 1999; Nagashima et al., 2000). If chromophobe RCCs have a significant range of sarcomatoid transformation, the prognosis may be worse (Aizawa et al., 1997; Hirokawa et al., 1998; Wilson et al., 1999; Nagashima et al., 2000). Renshaw et al. (1996) reported that large tumors (more than 8 cm in diameter) and those with coexistent papillary RCCs may cause metastasis.

Conclusions and perspectives

On the basis of the above-described findings, we can regard chromophobe RCCs as a distinct entity in both clinico-pathological and genetic aspects. However, chromophobe RCCs are sometimes encountered that are difficult to distinguish histologically from oncocytomas. Chromophobe RCCs and oncocytomas are both derived from intercalated cells of the collecting duct system (Ortmann et al., 1988, 1991; Störkel et al., 1988, 1989). Also, some cases of coexistent chromophobe RCC and oncoytoma, designated "renal oncocytosis" by Tickoo et al. (1999), have recently been reported. Furthermore, both chromophobe RCCs and oncocytomas show mitochondrial DNA alterations (Kovacs et al., 1989, 1992; Welter et al., 1989). Although the existence of a disease designated "chromophobe adenoma" has recently been suggested, this concept is still not widely accepted (Dujkhuizen et al., 1997; van den Berg, 1997). On the other hand, cases of oncocytoma with metastasis in a large series studied by Perez-Ordonez et al. (1997) have also been reported despite the strict histological criteria for oncocytomas. Additionally, the key gene (probably tumor supressor gene) causing chromophobe RCCs has not yet been identified, although Contractor et al. (1997) have reported that mutation of p53 occurs exclusively in chromophobe RCCs. Therefore, further investigations will be required to elucidate the relationship between chromophobe RCCs and oncocytomas and to confirm whether the concept of "chromophobe adenoma" actually exists or not.

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