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## *Review*

# Review of metanephric adenoma of the kidney with focus on clinical and pathobiological aspects

**N. Kuroda, M. Toi, M.Hiroi and H. Enzan**
First Department of Pathology, Kochi Medical School, Kohasu, Oko-cho, Nankoku City, Kochi, Japan

**Summary.** The concept of metanephric adenoma has become established in recent years. Metanephric adenoma is a rare neoplasm. Macroscopically, the cut surface of the tumor displays a tan to gray or yellow color, and tumors generally form well-circumscribed masses. Histologically, tumors are composed of small epithelial cells that form small acini. Glomeruloid bodies, which are composed of lobulated papillary projections, are occasionally seen. Although there have been few studies using chromosomal analysis, two recent studies have shown partial monosomy or LOH of 2p. On the other hand, the concept of metanephric tumors has recently become broadened. These tumors include metanephric adenomas, adenofibromas and stromal tumors, and they compose a continuous histological spectrum. Therefore, further studies on various aspects are needed to identify the gene responsible for the occurrence of metanephric tumors and, furthermore, to clarify the association among the three types of metanephric tumors.

**Key words:** Renal oncocytomas, Pathology, Chromosomal abonormalities

### History of the establishment of the disease entity

Metanephric adenoma was first described as a bilateral and diffuse tumor in a 7-year-old boy by Bove et al. in 1979. Pages and Granier proposed the name nephrogenic nephroma in 1980. The concept of metanephric adenoma was recognized as a distinct entity in a retrospective study of adult-onset Wilms' tumor by Mostofi et al. in 1988. This disease is also known as embryonal adenoma (Werbrouck et al., 1990; Perlman et al., 1995; Zafar et al., 1997). If the tumor is characterized by proliferation of spindle cells surrounding multifocal nodules of epithelial cells, it should be designated as a nephrogenic adenofibroma or metanephric adenofibroma (Henniger and Beckwith, 1992; Shek et al., 1999). Argani and Beckwith have recently described another renal tumor designated as a metanephric stromal tumor that consists purely of a mesenchymal component without an epithelial component (Argani and Beckwith, 2000). Pathologists should consider that the spectrum of these three metanephric tumors is morphologically continuous (Argani and Beckwith, 2000).

*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

### Epidemiology

Metanephric adenoma is a rare neoplasm (Fleming and O'Donnell, 2000). Metanephric adenomas generally occur in adults, particularly in middle-aged women (male:female = 1:2-6), but also occur in children (Davis et al., 1995; Jones et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998). The mean age and age range of patients with metanephric adenoma are 41 years and 5-83 years, respectively, in a large series studied by Davis et al. (1995) and 48.6 years and 38-64 years, respectively, in a large series studied by Jones et al. (1995).

### Clinical signs and symptoms

Most tumors are incidentally discovered during detailed examinations for other problems, including polycythemia, or during physical checkups. Abdominal or flank pain, hematuria and palpable mass are frequently presented. Some patients complain of fever (Davis et al., 1995; Jones et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998).

### Laboratory data

Results of the blood examinations in some patients with metanephric adenoma show increased number of erythrocytes (polycythemia) (Henninger and Beckwith,

1992; Davis et al., 1995; Grignon and Eble, 1998).

## Radiological findings

Imaging techniques such as ultrasonography and computerized tomography (CT) scan reveal well-circumscribed renal lesions (Werbrouck et al., 1990; Perlman et al., 1995; Zafar et al., 1997). A renal arteriogram of the tumor generally shows hypovascularity (Werbrouck et al., 1990; Nagashima et al., 1991; Ban et al., 1996).

## Pathological findings

### *Macroscopic findings*

The mean size and range of sizes of the tumor were 5.5 cm and 0.3-15 cm, respectively, in a study by Davis et al. (1995) and 4.7 cm and 0.6-8 cm, respectively, in a study by Jones et al. (1995). Bouzourene et al. (1997) reported a case with a largest tumor measuring 20x19x15 cm that was previously described. The cut surface of a metanephric adenoma is tan to gray or yellow in color, and tumors generally form well demarcated masses (Davis et al., 1995; Jones et al., 1995; Perlman et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998). Many tumors have no fibrous capsules, but some tumors do possess fibrous capsules (Werbrouck et al., 1990; Nagashima et al., 1991; Davis et al., 1995; Jones et al., 1995; Perlman et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998). Hemorrhage and necrosis in larger tumors are common (Davis et al., 1995). Protrusion above the renal surface may be seen, but extrarenal invasion is not seen (Werbrouck et al., 1990; Nagashima et al., 1991; Davis et al., 1995; Jones et al., 1995; Perlman et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998).

### *Microscopic findings*

Typically, tumors are composed of small epithelial cells that form small acini. Glomeruloid bodies, which are composed of lobulated papillary projections, are frequently observed (Werbrouck et al., 1990; Nagashima et al., 1991; Davis et al., 1995; Jones et al., 1995; Strong and Ro, 1996; Zafar et al., 1997; Grignon and Eble, 1998). Polypoid and microcystic growth patterns are also seen (Davis et al., 1995). Tumor cells have uniformly small and oval-to-round nuclei, small and indistinct nucleoli, and scanty and basophilic cytoplasm (Werbrouck et al., 1990; Nagashima et al., 1991; Davis et al., 1995; Jones et al., 1995; Perlman et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998). Nuclei with coffee bean-like grooves are also seen. Scar formation and calcification are often observed (Davis et al., 1995; Grignon and Eble., 1998). The stroma is generally acellular, edematous or hyalinous (Davis et al., 1995; Jones et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998). Myxoid degeneration may also be present (Grignon and Eble, 1998). Pleomorphism is absent. Abnormal mitotic figures are never seen (Davis et al., 1995; Jones et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998).

### *Histochemical and immunohistochemical findings*

Tumor cells show weakly positive reaction to PAS staining. As for lectin histochemical study, tumors showing a positive reaction to peanut agglutinin (PNA), *Dolichos biflorus* agglutinin (DBA) and soybean

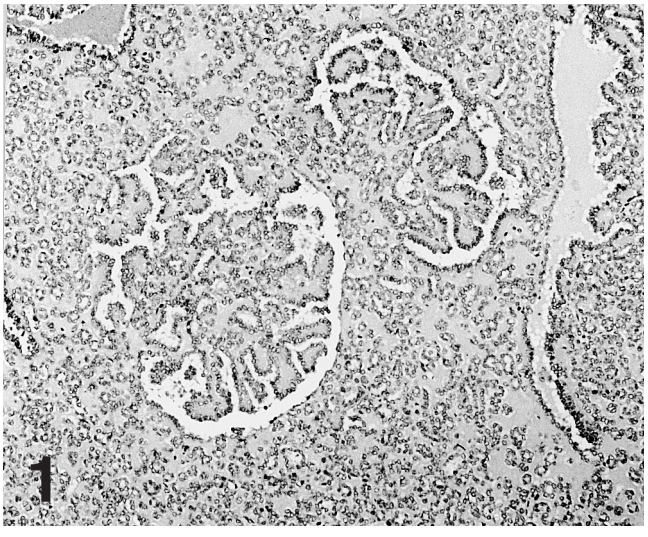


**Fig. 1.** Tumor cells proliferate with the formation of small acini. Glomeruloid bodies, which are composed of lobulated papillary projections, are also seen. x 25

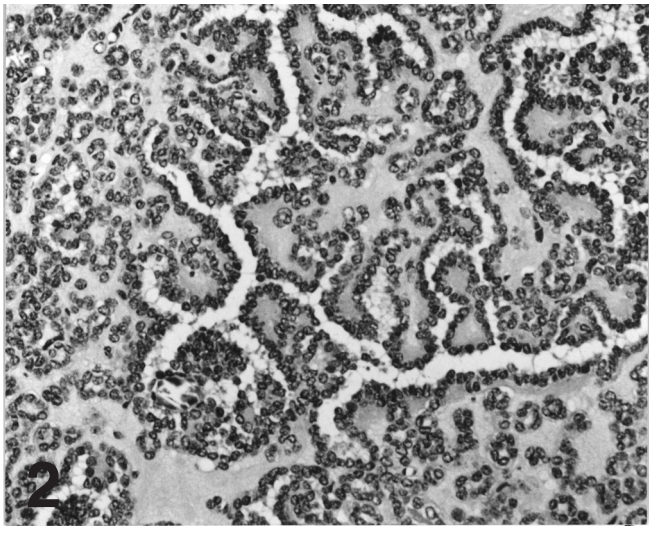


**Fig. 2.** Tumor cells have uniformly small and oval-to-round nuclei, small and indistinct nucleoli, and scanty cytoplasm. The stroma is edematous. x 50

agglutuinin (SBA) have been reported (Nagashima et al., 1991; Ban et al., 1996). Various immunoreactivities for divergent antigens (cytokeratin, EMA, S-100, etc.) have been reported (Henninger and Beckwith, 1992; Ban et al., 1996). Tumor cells are often positive for vimentin and Leu7 (Jones et al., 1995; Strong and Ro, 1996). Tumor cells also demonstrate an occasional positive reaction to WT1 and CD57, as do maturing Wilms' tumors and nephrogenic rests (Muir et al., 2001).

*Cytological findings*

Cellular smears show small blue cells with scanty cytoplasm, evenly distributed and fine chromomatin in the nulceus, and occasionally small nucleoli. Furthermore, these cells are arranged in a vague rosette-like pattern (Zafar et al., 1997; Xu et al., 2000). In cell blocks, on the other hand, these cells are arranged as compact, primitive, tubular rosette or, rarely, more-solid clusters (Zafar et al., 1997; Xu et al., 2000).

*Ultrastructural findings*

The tumor cells contain various amounts of mitochondria, rough endoplasmic reticulum, lysosomes, ribosomes and lipid droplets.Tumor cells are surrounded by a basement membrane, and nuclear polarity is poor. Structures such as desmosomes or tight junctions are also observed. Short microvilli are present (Nagashima et al., 1991; Jones et al., 1995; Ban et al., 1996; Strong and Ro, 1996; Baschinsky and Niemann, 1999).

**Flow cytometric analysis**

DNA content analysis of metanephric adenomas reveals diploid histograms (Jones et al., 1995; Nonomura et al., 1995a; Strong and Ro, 1996).

**Chromosomal abnormalities (karyotyping, fluorescence in situ hybridization (FISH) , comparative genomic hybridizazion (CGH) and microsatellite analysis)**

Cytogenetic analysis in some cases has revealed normal karyotypes (Jones et al., 1995; Perlman et al., 1995; Gatalica et al., 1996; Strong and Ro, 1996; Granter et al., 1997). However, Brown et al. (1996) reported a case with gain of chromsosomes 7 and 17 and loss of chromosome Y, and they later found combined trisomy of chromosome 7 and 17 in 8 out of 11 tumors using FISH. They have thus shown a close relationship between metanephric adenomas and papillary renal cell carcinomas (Brown et al., 1996, 1997) However, some investigators consider that tumors designated as metanephric adenomas by Brown et al. (1996, 1997) may be solid variants of papillary renal cell carcinomas. In constrast to reports by Brown et al. (1996, 1997), Renshaw et al. (1997, 2000) found, by using FISH, a disomic pattern (two copies) of chromosomes 7 and 17 in two cases, one in a child and one in an adult. Tsuji et al. (1999) and Birgisson et al. (1999) also reported a case showing similar results to those of the cases studied by Renshaw et al. (2000). Stumm et al. (1999) found a case with partial monosomy 2p in a case using karotyping, FISH and CGH. Pesti et al. (2001) found by microsatellite analysis of 12 cases that allelic loss frequently occurs in the loci between D2S2153 and D2S380 on 2p13.

**Differential diagnosis in histopathology**

Distinction from nephrogenic rests (nodular renal blastema), Wilms' tumors, renal cell carcinomas (RCCs) and metastatic cancers is required (Brisgotti et al., 1992; Nonomura et al., 1995b; Renshaw et al., 1997; Grignon and Ro, 1998). Nephrogenic rests do not form macroscopically evident masses, and classical Wilms' tumor is multinodular. Furthermore, both nephrogenic rests and Wilms' tumor microscopically contain a blastema component, whereas metanephric adenomas do not possess a blastema component. Moreover, metanephric adenomas are composed of uniform-sized cells and lack abnormal mitotic figures and marked cytological atypia. In the distinction from renal cell carcinomas, particular attention must be paid to papillary carcinomas. If fibrovascular cores, a number of macrophages or hemosiderins in the stroma and marked cytological atypia are present, the tumor is more likely to be a papillary RCC than metanephric adenoma (Granter et al., 1997). Metanephric adenomas must also be distinguished from metastatic cancers, particularly from those in the thyroid gland or lung (Granter et al., 1997; Renshaw et al., 1997; Pins et al., 1999). In cytology, metanephric adenomas also show similar characteristics (nuclear grooves and intranuclear inclusions) to those of papillary carcinoma of the thyroid gland (Granter et al., 1997; Renshaw et al., 1997). In such a situation, clinical information is very important. Immunohistochemical study of thyroid transcription factor 1 (TTF-1) may also provide useful information.

The age of disease onset is important information for differential diagnosis (Nonomura et al., 1995b). For example, it is known that 90% of Wilms' tumors occur in children younger than the age of 6 years (Renshaw et al., 2000).

Chromosomal analysis may also be helpful (Granter et al., 1997; Renshaw et al., 1997, 2000). Wilms' tumors show alterations at chromosome 11p. Conventional RCCs and papillary renal tumors are characterized by loss of chromosome 3p and by trisomy of chromosome 7 and 17, and loss of the Y chromosome, respectively (Kovacs, 1989, 1990, 1993a,b; Kovacs et al., 1997, 1998; Kovacs, 1989; Kovacs and Frisch, 1989; Kovacs and Kung, 1991).

**Treatment and prognosis**

Werbrouck et al. (1990) reported that nephrectomy

alone or even simple enuclation is justifiable. Almost all metanephric adenomas show a favorable clinical course (Davis et al., 1995; Jones et al., 1995; Strong and Ro, 1996; Grignon and Eble, 1998). However, Renshaw et al. (2000) reported a case in a 7-year-old child that metastasized to regional lymph nodes.

## Conclusions and perspectives

Based on previously reported results, metanephric adenoma can be regarded as a distinct entity. However, genetic studies on metanephric tumors have been limited because of the rarity of such tumors. Therefore, further studies on various aspects of metanephric tumors, including adenoma, adenofibroma and stromal tumors are needed to clarify the relationship among these three types of tumor and to identify the key gene that causes metanephric tumors.

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