Histol Histopathol (2005) 20: 221-224

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Histology and Histopathology

Cellular and Molecular Biology

Review

Review of mucinous tubular and spindle-cell carcinoma of the kidney with a focus on clinical and pathobiological aspects

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

[1]Department of Pathology, Program of Bioregulation and Genetics and

[2]Department of Urology, Program of Tumor Biology and Regulation, Kochi Medical School, Kochi University, Kochi, Japan

Summary. Recently, the characterization of mucinous tubular and spindle-cell carcinoma (MTSCC) has been established. MTSCC predominantly occurs in females. This tumor is histologically characterized by eosinophilic cytoplasm, elongated and anastomosing tubules, myxomatous stroma and low-grade nuclear cytology. Proliferation of spindle cells or foci of clear cells are also observed. Histochemically, the myxomatous stroma exhibits a positive reaction for alcian blue and colloidal iron stainings. Ultrastructurally, short microvilli are focally observed and junctional complexes are present. Recently, multiple losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15 and 22 in MTSCC have been elucidated by using comparative genomic hybridization. The prognosis of MTSCC is generally favorable, but some cases may show local recurrence or metastasis. Some cases with MTSCC seem to show overlapping histology with low-grade collecting-duct carcinoma. Therefore, further investigation will be needed to elucidate pathobiological characteristics of MTSCC.

Key words: Mucinous tubular and spindle cell carcinoma, Kidney, Pathology

History of the establishment of the disease

Several renal tumors with characteristic histology have been reported as unclassified renal cell carcinoma (RCC) (Ordonez et al, 1996; Lloreta et al., 1998; He et al., 1998; Otani et al., 2001). In 2001, Parawani et al. characterized four cases as low-grade myxoid renal epithelial neoplasm with distal nephron differentiation and proposed that this tumor was a distinct entity from the hitherto established renal tumors. Subsequently, in 2002, Razoky et al. (2002) and Hes et al. (2002) reported detailed histological or genetic features of five and eleven cases, respectively. In the recent WHO classification, this tumor was introduced as mucinous tubular and spindle-cell carcinoma (MTSCC) (Srigley, 2004).

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

Epidemiology

Most studies have reported a sexual predisposition in females (Srigley et al., 1999, 2002; Parwani et al., 2001; Razaky et al., 2002; Aubert et al., 2004). In contrast, according to the article by Hes et al. (2002), there is no sexual predominance. The mean age and age range of patients with MTSCC was 53 years and 17-82 years, respectively, in a large series studied by Srigley et al. (2002) and 56.8 years and 22-65 years, respectively, in a large series studied by Hes et al. (2002)

Clinical symptoms and signs

Most MTSCC tumors are incidentally discovered (Leroy et al., 2002; Kuroda et al., 2004, Srigley, 2004). However, some tumors may exhibit typical symptoms of RCC, such as hematuria, flank pain or abdominal mass (Leroy et al., 2002; Parwani et al., 2001; Hes et al., 2002). Some cases also exhibit nephrolithiasis (Hes et al., 2002).

Radiological findings

Ultrasound sonography, computed tomography (CT) and magnetic resonance imaging (MRI) examinations generally disclose a mass protruding from the kidney surface (Otani et al., 2001; Aubert et al., 2004; Hara et al., 2004). Angiography has revealed hypovascular or avascular lesions on some tumors (He et al., 1998;

Aubert et al., 2004).

Pathological Findings

Macroscopic findings

Large MTSCC tumors extend from the renal cortex to the renal medulla, protruding into the extra-renal tissue (He et al., 1998; Lloreta et al., 1998; Otani et al., 2001; Hara et al., 2004; Kuroda et al., 2004). In contrast, smaller tumors may be restricted to the renal medulla (Parwani et al., 2001; Leroy et al., 2002; Aubert et al., 2004). Tumor borders are generally well defined, but tumors generally have no capsules (Hes et al., 2002; Razoky et al., 2002; Aubert et al., 2004). The cut surface of tumors is white, grey-white, light tan, brown or yellow in color (Hes et al., 2002; Razoky et al., 2002; Aubert et al., 2004). Tumors display a solid consistency and cystic change is rare (Parwani et al., 2001; Razoky et al., 2002). Focal hemorrhage is frequently seen and hemorrhage is rarely extensive (Parwani et al., 2001; Hes et al., 2002; Razoky et al., 2002). Necrotic foci are sometimes observed (Parwani et al., 2001; Hes et al., 2002). Involvement into extra-renal tissue or the renal vein is very rare (Razoky et al., 2002; Aubert et al., 2004).

Microscopic findings

Histologically, tumors generally consist of cuboidal and spindle cells (He et al., 1998; Otani et al., 2001; Hes et al., 2002; Razoky et al., 2004; Srigley et al., 2004). Growth patterns, including tubular (Fig. 1), trabecular or cord-like (Fig. 2), and solid ones are observed (He et al., 1998; Otani et al., 2001; Hes et al., 2002; Razoky et al., 2002; Kuroda et al., 2004; Srigley, 2004). Interconnecting or anastomosing tubules are often identified (He et al., 1998; Parwani et al., 2001; Leroy et al., 2002, Hes et al., 2002; Razoky et al., 2002; Kuroda et al., 2004, Srigley, 2004). A papillary growth pattern or glomeruloid-like features (He et al., 1998; Kuroda et al., 2004) may be observed. Spindle-cell foci are frequently seen (Fig. 3) and simulate features of smooth muscle (Hes et al., 2002; Razoky et al., 2002; Srigley, 2004). Many neoplastic cells show eosinophilic cytoplasm, although foci may be seen in clear cells (Parwani et al., 2001; Hes et al., 2002; Razoky et al., 2002; Aubert et al., 2004; Kuroda et al., 2004). Rarely, foci of clear cells may resemble the histological features of clear cell carcinoma (Fig. 4) (Hes et al., 2002; Kuroda et al., 2004). Nuclei generally show low-grade atypia (Razoky et al., 2002; Srigley, 2004). Nuclei are generally round and centrally located (Leroy et al., 2002; Razoky et al., 2002; Kuroda et al., 2004). Single small to moderate-sized nucleoli are occasionally seen (Razoky et al., 2002). Mitotic figures are rare and abnormal mitoses are never observed (Parwani et al., 2001; Hes et al., 2002). The stroma is occasionally myxomatous or edematous (Parwani et al., 2001; Leroy et al., 2002; Razoky et al., 2002; Kuroda et al., 2004). Infiltration of plasma cells, mast cells or macrophages is frequently seen in the myxomatous stroma (Parwani et al., 2001; Leroy et al., 2002; Razoky et al., 2002; Aubert et al., 2004; Kuroda et al., 2004).

Histochemical findings

The myxomatous stroma of MTSCC exhibits a positive reaction for alcian blue and colloidal iron stains (Parwani et al., 2001; Leroy et al., 2002; Razoky et al., 2002; Kuroda et al., 2004), and the stroma is positive for periodic acid-Schiff (PAS) stain in some reports (He et al., 1998; Leroy et al., 2002; Aubert et al., 2004), but negative in others (Razoky et al., 2002). Additionally,

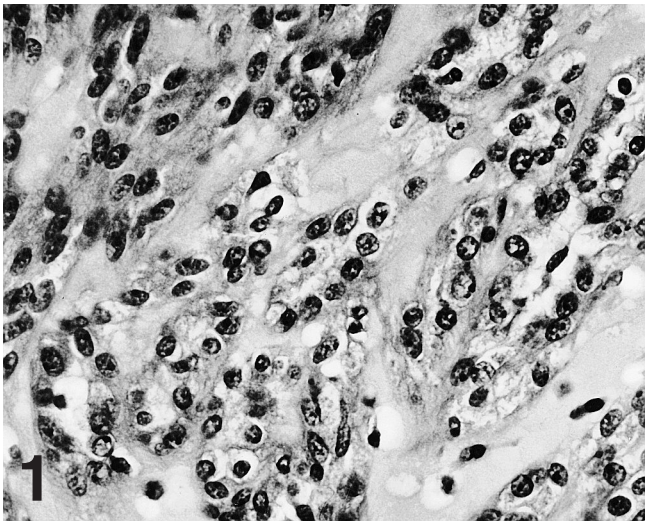

Fig. 1. Microscopic findings of MTSCC. Cuboidal neoplastic cells proliferating with tubules. x 50

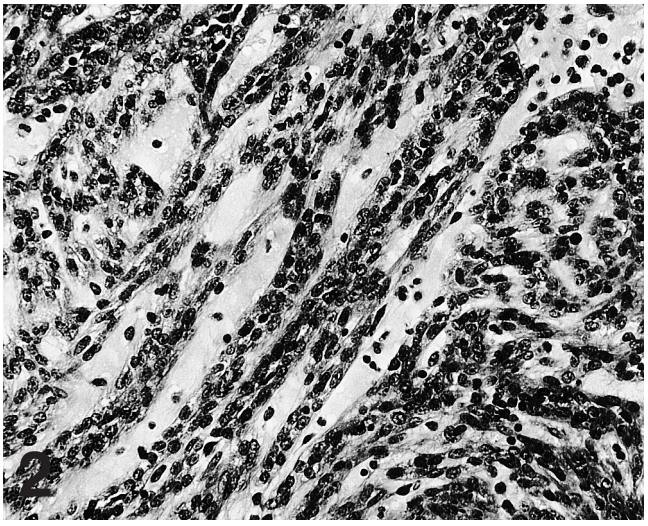

Fig. 2. Microscopic findings of MTSCC. A cord-like proliferating pattern is observed in the myxomatous stroma. x 25

the myxomatous stroma may exhibit a weak positive reaction for mucicarmine stain (Parwani et al., 2001).

Immunohistochemical findings

Many MTSCC tumors exhibit positive reactions for vimentin, epithelial membrane antigen (EMA) and cytokeratin cocktail AE1/AE3 (Srigley et al., 1999; Ohtani 2001; Parwani et al., 2001; Hes et al., 2002; Leroy et al., 2002; Razoky et al., 2002; Aubert et al., 2004). High-molecular-weight cytokeratin 34ßE12, cytokeratins 7, 8 and 18, CAM 5.2 or *Ulex Europeus* agglutinin-1 (UEA-1) are frequently expressed (Srigley et al., 1999, 2002; Parwani et al., 2001; Leroy et al., 2002; Hes et al., 2002; Razoky et al., 2002; Aubert et al., 2004). The MIB-1 labeling index is generally very low (Leroy et al., 2002; Razoky et al., 2002; Hara et al., 2004)

Ultrastructural findings

Utrastructurally, focal short microvilli are generally observed along glandular lumens (He et al., 1998; Lloreta et al., 1998; Otani et al., 2001; Kuroda et al., 2004; Srigley, 2004). Junctional complexes such as tight junctions, intermediate junctions or desmosomes may be seen (He et al., 1998; Srigley, 2004). Basal lamina may also be observed (Otani et al., 2001). The abundance of mitochondria, rough endoplasmic reticulum or polyribosomes varies from case to case (Lloreta et al., 1998; Parwani et al., 2001; Hes et al., 2002; Kuroda et al., 2004). Lipids and glycogen are rarely observed (Lloreta et al., 1998; Kuroda et al., 2004). Interdigitations between tumor cells may be sometimes observed (Parwani et al., 2001; Kuroda et al., 2004). The nuclear membranes of neoplastic cells are frequently invaginated (Kuroda et al., 2004).

Chromosomal abnormalities and other genetic features

Razoky et al. (2002) elucidated multiple losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15 and 22 using comparative genomic hybridization in five cases with MTSCC. Although in the abstract form, Srigley et al. (2002) reported frequent losses of chromosomes 1, 4q, 6, 8p, 9q, 11q, 13, 14 and l5, and gains of chromosomes 11q, 12q, 16q, 17 and 20q. Additionally, using a FISH analysis, they showed that tumors had no *VHL* deletions. Weber et al. (2003) reported that tumors do not exhibit a loss of chromosome 3p or a mutation in the *VHL* gene, which are frequently observed in conventional RCC.

Differential diagnosis in histopathology

A differential diagnosis from metanephric adenoma, oncocytomas, conventional RCC, papillary RCC, low-grade collecting-duct carcinoma (CDC), sarcomatoid RCC, juxtaglomerular cell tumor and angiomyolipoma is necessary for the proper identification of the tumor. The macroscopical findings of MTSCC may resemble those of metanephric adenoma (Kuroda et al., 2003a, 2004). In metanephric adenoma, neoplastic cells exhibit a basophilic cytoplasm and form small acini (Kuroda et al., 2003a). Additionally, psammoma bodies are occasionally seen in the stroma (Perez-Montiel and Suster, 2003). In oncotocytoma, the cut surface is mahogany brown and a nesting growth pattern is histologically characteristic (Kuroda et al., 2003c). In conventional and papillary RCCs, the myxomatous stroma is absent. In low-grade CDC, a histological cystic change is frequently seen (MacLennan et al., 1997). However, overlapping cases exhibiting some features of both tumors have been reported. In sarcomatoid RCC, the cytological atypia is marked and pleomorphism is

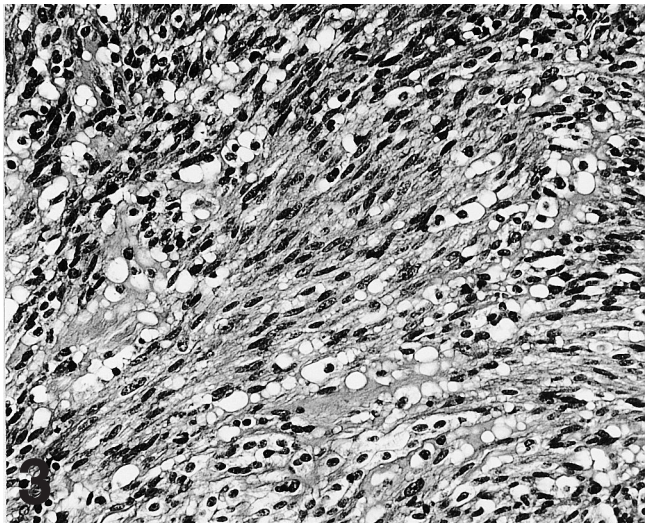

Fig. 3. Microscopic findings of MTSCC. Proliferation of spindle cells is seen. x 25

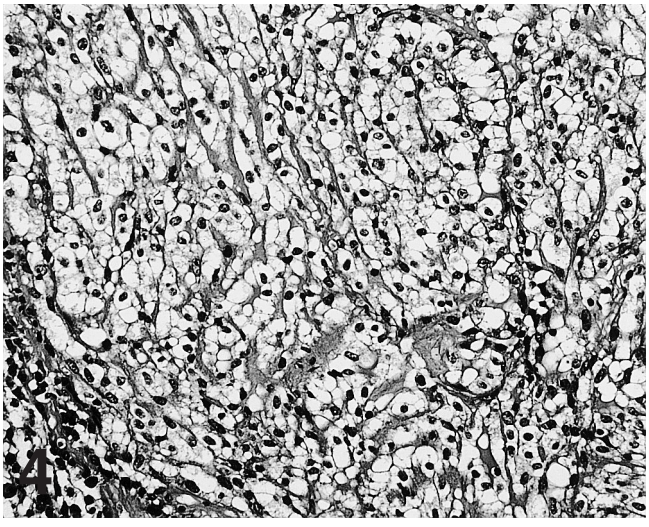

Fig. 4. Microscopic findings of MTSCC. Focus of clear cells resembling clear cell carcinoma is observed. x 25

occasionally prominent (Kuroda et al., 2003b). Rhomboid-shaped renin granules are observed in the cytoplasm of juxtaglomerular cell tumors (Martin et al., 2001). In angiomyolipoma, mature fat tissue and vascular structure are observed in the neoplastic component, and neoplastic cells exhibit a positive reaction for HMB-45 (Kuroda et al., 2004).

Prognosis

Tumor prognosis is generally favorable. Many investigators have reported that most tumors generally show neither local recurrence nor metastasis (Parwani et al., 2001; Leroy et al., 2002). However, a few cases with local recurrence (Razoky et al., 2002) or metastasis to lymph nodes (Hes et al., 2002) have been reported.

Conclusions and Perspectives

Recently, MTSCC has been established as a distinct entity from hitherto reported renal tumors based on the histological and genetic aspects. Inclusion of the loop of Henle (Srigley, 1999, 2002; Weber et al., 2003) or collecting duct (Razoky et al., 20002; Kuroda et al., 2004) has been suggested as the MTSCC phenotype but this view is debatable. However, some overlapping between MTSCC and low-grade CDC has been reported by MacLennan et al. (1997). Additionally, we have found a case of MTSCC with neuroendocrine differentiation using immunohistochemical and ultrastructural methods (Kuroda et al., 2004). Therefore, we suggest that some tumors of this entity may exhibit low-grade neuroendocrine carcinomas. Therefore, further examinations will be required in order to clarify the relationship between this tumor and low-grade CDC and the pathobiological nature of this tumor.

Acknowledgements. This work was supported by a grant for Encouragement of Young Scientists (14770074) from the Ministry of Education, Science and Culture, Japan.

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Accepted August 10, 2004