Summary. In recent years, the concept of collecting duct carcinoma (CDC) has been established. CDCs constitute about 0.4 to 2% of RCCs. Macroscopically, CDCs occur in the renal medulla. On the cut surface, they are generally firm, white or grey and poorly circumscribed. Histologically, CDCs are characterized by various cytological and histological appearances. Furthermore, desmoplastic stromal reaction around the tumor and atypical hyperplastic changes or carcinoma in situ in the adjacent medullary collecting duct are frequently observed. Histological distinction from papillary RCCs is most important, because both tumors share some structural and histochemical features, and it seems that some investigators have confused diagnostic criteria for CDCs. On the other hand, the concept of medullary carcinoma, which preferentially occurs in a black race and shows histological features similar to those of CDC, has also recently been established. Although there have been few studies on chromosomal abnormalities of CDCs and consistent abnormalities have not been identified, a recent study using microsatellite analysis has shown a high frequency (60%) of LOH in 1q32.1-32.2. Further studies are needed to elucidate the genetic characteristics of CDCs and to determine the relationship or difference between CDCs and medullary carcinomas.

Key words: Collecting duct carcinomas, Pathology, Chromosomal abnormalities

History of the establishment of the disease concept

Mancilla-Jimenez and Stanley (1976) reported that atypical hyperplastic changes of adjacent collecting ducts were present in 3 out of 34 cases of papillary renal cell carcinoma (RCC) and suggested that some papillary RCCs may arise from collecting ducts. Some carcinomas of the kidney, suggestive of collecting (Bellini) duct origin have since been reported (Cromie et al., 1979; O'Brien and Bedard, 1980; Hai and Diaz-Perez, 1982; Lack et al., 1985). Thoenes et al. (1986) categorized chromophobe RCCs and collecting (Bellini) duct carcinomas (CDCs) as new distinct entities into their classification system of renal tumors. Furthermore, in the same year, Fleming and Lewi (1986) described in detail pathological (macroscopic and microscopic) findings of six cases of CDC. In recent classifications, CDCs have also been recognized as a different entity from conventional, papillary and chromophobe RCCs (Kovacs et al., 1997; Störkel et al., 1997).

Epidemiology

CDCs constitute about 0.4 to 2% of RCCs (Fleming and Lewi, 1986; Rumpelt et al., 1991). There is a male predominance (male:female = ratio: 1.7-2:1) in frequency of occurrence (Kennedy et al., 1990; Dimopoulous et al., 1993; Amin et al., 1997; Srigley and Eble, 1998). The average age and range of ages of patients are about 55 years and 13-83 years, respectively (Amin et al., 1997; Srigley and Eble, 1998). Some studies have shown that CDCs occur more frequently than conventional RCCs do in relatively young adults (O’Brien and Bedard, 1980; Lack et al., 1985; Kennedy et al., 1990; Dimopoulous et al., 1993; Olivere et al., 1999).

Clinical symptoms and signs

Symptoms or signs, including abdominal pain, flank mass and hematuria, are common. General symptoms such as weight loss, fever and anorexia, which are suggestive of metastasis, are also occasionally present (Amin et al., 1997; Srigley and Eble, 1998).

Other clinical settings

A CDC case in a horseshoe kidney and cases of coexistent conventional or papillary RCC and CDC have recently been reported (Dodd et al., 1995; Auguet et al., 2000; Daniel et al., 2001). Patients with CDCs usually
have a family history of associated malignancies, including colon, pancreas, lung, ovary and uterus malignancies (Dimopoulous et al., 1993; Srigley and Eble, 1998).

**Pathological findings**

**Macroscopic findings**

CDCs arise in the renal medulla, but irregular extensions into the adjacent renal cortex may be present in cases of large tumors (Fleming and Lewi, 1986; Kennedy et al., 1990; Dimopoulous et al., 1993; Mattelaer et al., 1996; Amin et al., 1997; Srigley and Eble, 1998). They are generally firm, white or grey, and poorly circumscribed (Fleming and Lewi, 1986; Kennedy et al., 1990; Dimopoulous et al., 1993; Mattelaer et al., 1996; Amin et al., 1997; Srigley and Eble, 1998). A grossly recognized cystic formation is rare but may be present in low-grade (well-differentiated) CDCs (Amin et al., 1997; MacLennan et al., 1997; Srigley and Eble, 1998). Hemorrhage and necrosis are not prominent (Fleming and Lewi, 1986). Invasion into a renal vein is sometimes observed (Rumpelt et al., 1991). Furthermore, local invasion into perirenal and renal sinus fat may be found (Srigley and Eble, 1998).

**Microscopic findings**

CDCs are characterized by various cytological and histological appearances (Rumpelt et al., 1991; Störkel, 1995, 1996). The tumor consists of an intermingling of clear, eosinophilic and basophilic cells (Rumpelt et al., 1991; Störkel, 1995, 1996). Hobnail cells are occasionally seen (Amin et al., 1997; Srigley and Eble, 1998). A variety of growth patterns, including tubular, papillary, microcystic-papillary, psuedopapillary, cribriform and solid patterns, are observed (Fig. 1) (Fleming and Lewi, 1986; Kennedy et al., 1990; Rumpelt et al., 1991; Dimopoulous et al., 1993; Amin et al., 1997; Srigley and Eble, 1998; Kuroda et al., 2001). Rumpelt et al. (1991) emphasized that the microcystic papillary pattern is diagnostically most important (Fig. 2). The tubular architecture is markedly irregular, and anastomosing glands are often observed (Fleming and Lewi, 1986). Nuclear atypia is prominent, and significant atypical mitotic figures are also present (Amin et al., 1997; Srigley and Eble, 1998). Desmoplastic stromal reaction and intensive inflammatory cell infiltration, especially by granulocytes, are observed in the tumor center or at the front of tumor invasion (Fig. 3) (Fleming and Lewi, 1986; Kennedy et al., 1990; Rumpelt et al., 1991; Dimopoulous et al., 1993; Störkel, 1995, 1996; Amin et al., 1997; Srigley and Eble, 1998; Kuroda et al., 2001). Atypical hyperplastic changes or carcinoma in situ may be present in the adjacent medullary collecting duct (Fig. 4) (Fleming and Lewi, 1986; Kennedy et al., 1990; Dimopoulous et al., 1993; Störkel, 1995, 1996; Amin et al., 1997; Srigley and Eble, 1998; Kuroda et al., 2001). Marked vascular and lymphatic invasion are common (Rumpelt et al., 1991; Srigley and Eble, 1998). These features are due to the predominance of a central location in CDCs. CDCs with sarcomatoid transformation have been noted (Rumpelt et al., 1991; Baer et al., 1993; Amin et al., 1997; Srigley and Eble, 1998).

**Histochemical and immunohistochemical findings**

The presence of mucin is confirmed by periodic acid-Schiff (PAS), alcian blue or mucicarmine stainings.

![Fig. 1. Proliferation of tumor cells in glands with marked cytological atypia is observed. x 50](image1)

![Fig. 2. Microcystic papillary projection of tumor cells. x 50](image2)
in some cases (Kennedy et al., 1990; Amin et al., 1997; Srigley and Eble, 1998). In lectin histochemistry, *Ulex europaeus* agglutinin-I (UEA-I) is commonly reactive (Rumpelt et al., 1991; Amin et al., 1997; Srigley and Eble, 1998). Peanut lectin is also often positive (Amin et al., 1997; Srigley and Eble, 1998). Immunohistochemically, high-molecular-weight keratin (34βE12, cytokeratin 19) is commonly immunoreactive, and vimentin may also be reactive (Rumpelt et al., 1991; Amin et al., 1997; Srigley and Eble, 1998).

**Ultrastructural findings**

Ultrastructurally, tumor cells have straight membranes with long range junctional complexes, which are characteristic of principal cells of the medullary duct (Rumpelt et al., 1991; Störkel, 1995, 1996). The cytoplasm has an abundance of organelles. Mitochondria occupy 10-30% of the cytoplasmic volume. The rough endoplasmic reticulum forms small strands. There are few glycogen particles and lipid droplets (Rumpelt et al., 1991).

**Cytological findings**

In voided urine, gland-like clusters of large cells with granular cytoplasm and prominent nucleoli are observed (Mauri et al., 1994). In intraoperative imprints, neoplastic cells with marked cytological atypia and tubular or papillary architecture, and fibrotic desmoplastic stroma are seen (Bejar et al., 1996). In smears by fine-needle aspiration biopsy, individual and small clusters of round-to-oval-shaped cells with small to moderate amounts of well-defined cytoplasm are observed. The nuclei are large and hyperchromatic with prominent single nucleoli and fine chromatin clearing (Layfield, 1994).

**Flow cytometric analysis**

Dimopoulos et al. (1993) reported that DNA content analysis revealed aneuploid histograms in five out of six CDCs and a diploid pattern in the remaining one.

**Chromosomal analysis (karyotyping and microsatellite analysis)**

In karyotyping, Füzesi et al. (1992) reported that all three CDCs showed monosomy of chromosomes 1, 6, 12, 15, 22. Gregori-Romero et al. (1996) reported three CDC cases showing different chromosomal abnormalities, one tumor demonstrating the same abnormalities as those of papillary RCC. However, they did not show an illustration of the tumor. Cavazzana et al. (1996) reported a case showing trisomies of chromosomes 4, 7, 8, 17 and 20. In microsatellite analysis, Schoenberg et al. (1995) reported that three out of six tumors in their series showed loss of heterozygosity in chromosome arms 8p and 13q. Polascik et al. (1996) found, using macrosatellite analysis of 18 CDCs, LOH in 1q, 6p, 8p and 21q in 57%, 45%, 40% and 40% of CDCs, respectively. Furthermore, Steiner et al. (1996) found, by high-density mapping of chromosome arm 1q, that nine (60%) out of thirteen CDCs showed LOH in 1q32.1-32.2.

**Differential diagnosis in histopathology**

The distinction from papillary RCCs, medullary carcinomas, conventional RCCs, transitional cell carcinoma, juxtaglomerular cell tumors and metastatic carcinoma originating from other sites should be considered (Amin et al., 1997; Srigley and Eble, 1998; Olivere et al., 1999). Distinguishing CDCs from papillary RCCs is most important, because both tumors...
share some pathological features, including a papillary architecture and positive reaction for distal nephron markers (Kennedy et al., 1990; Rumpelt et al., 1991; Dimopoulous et al., 1993; Hughson et al., 1993; Mattelaer et al., 1996; Amin et al., 1997; Störkel, 1995, 1996). Furthermore, atypical hyperplastic changes of adjacent collecting ducts and desmoplasic reaction around the tumor are important clues for diagnosis of CDCs (Fleming and Lewi, 1986; Kennedy et al., 1990; Dimopoulous et al., 1993; Amin et al., 1997; Srigley and Eble, 1998). Histochemically, the presence of mucin detected by PAS, alcian blue or mucicarmine generally suggests CDC, but several papillary RCCs also possess mucin (Grignon et al., 1988; Kennedy et al., 1990; Amin et al., 1997; Srigley and Eble, 1998; Val-Bernal et al., 1999). Immunohistochemically, papillary RCCs are frequently positive for cytokeratin 7, whereas CDCs display positive reactions for UEA-I and high-molecular-weight cytokeratin (34bE12) (Rumpelt et al., 1991; Gatalica et al., 1995; Amin et al., 1997; Delahunt and Eble, 1997; Srigley and Eble, 1998). Immunohistochemistry for CD9 may be helpful in some cases for distinction between papillary RCCs and CDCs (Kuroda et al., 2001). Chromosomal analysis may also be useful. Papillary RCCs generally show trisomies of chromosomes 7 and 17 and loss of Y chromosome (Kovacs et al., 1997). In any case, a comprehensive evaluation of various findings is important. Renal medullary carcinomas frequently occur in patients of black races with sickle cell trait and histologically a loose reticular pattern of growth reminiscent of a yolk sac tumor with a compact adenoid-cystic pattern (Davis et al., 1995). However, some investigators consider medullary carcinoma as a subtype of CDCs (Amin et al., 1997). In conventional RCCs, the cut surface is typically yellow and tumor cells contain abundant glycogens and lipid droplets as determined by histochemical and ultrastructural examinations, respectively. Deletion of chromosome arm 3p is frequently seen (Kovacs et al., 1997). In transitional cell carcinomas, tumor cells sometimes exhibit epithelial involvement in collecting ducts. Therefore, there is a possibility that this finding may lead to pathological diagnosis of "atypical hyperplastic change or carcinoma in situ of collecting ducts". Transitional cell carcinoma cells are immunohistochemically negative for vimentin and positive for cytokeratin 13 in most cases, whereas CDCs exhibit opposite results (Rumpelt et al., 1991). In juxtaglomerular cell tumors, the tumor is macroscopically well-circumscribed. Histologically, a significant amount of mast cells is observed in the stroma. Furthermore, tumor cells contain renin granules as demonstrated by immunohistochemistry or electron microscopy (Kuroda et al., 2000). Finally, it is important to distinguish CDCs from metastatic cancers, especially adenocarcinomas producing mucin, namely, digestive tract cancers (Srigley and Eble, 1998; Olivere et al., 1999). In such settings, clinical information on the past history of cancers originating from other sites is very important.

**Treatment and prognosis**

Despite the availability of various systemic therapies, including radical nephrectomy, chemotherapy, radiation and immunotherapy, the prognosis is generally worse compared with that of other RCCs (Kennedy et al., 1990; Rumpelt et al., 1991; Dimopoulous et al., 1993; Mattelaer et al., 1996; Amin et al., 1997; Srigley and Eble, 1998). However, the prognosis may be favorable in some CDC cases or low-grade (well-differentiated) CDCs (Fleming and Lewi, 1986; MacLennan et al., 1997). Many patients with CDCs already have invasion into other sites or metastasis when the diagnosis is established (Kennedy et al., 1990; Amin et al., 1997; Srigley and Eble, 1998). Metastases to regional lymph nodes, bone, adrenal glands, lung and skin have been reported in CDCs (Dimopoulous et al., 1993). Meninges are also occasionally metastatic sites (Olivere et al., 1999). About two thirds of patients with CDCs die of carcinoma within two years of detection of the CDC (Dimopoulous et al., 1993; Amin et al., 1997).

**Conclusions and perspectives**

Although many CDCs have relatively unique histological characteristics, some CDCs have the same structural configurations and immunohistochemical findings as those of papillary RCCs (Kuroda et al., 2001). Therefore, it seems that some investigators have confused diagnostic criteria for distinction between CDCs and papillary RCCs (Kutta et al., 1993; Fukuya et al., 1996; Matsumoto et al., 2001). Since CDCs are very rare in renal tumors and generally have an abundant stroma, which is basically different from other RCCs and causes contamination of non-neoplastic tissue, there has so far been little genetic research on CDCs. Further investigation is needed to elucidate the genetic characteristics of CDCs and to determine the relationship between CDCs and medullary carcinomas.

**References**


Collecting duct carcinoma


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