1 Histopathological Classification

Shigeki Tomita, Yoshihiko Ueda and Takahiro Fujimori

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1.1 Introduction

Among all benign and malignant tumors, few are the result of kidney cancer. Cancer of the kidney accounts for only about 3% of all cancers in adults, with about 36,000 cases expected in the United States in 2004 (Jemal et al. 2004).

S. Tomita, MD, PhD
Assistant Professor of Pathology, Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine; Department of Surgical Pathology, Dokkyo University Hospital, 880 Kitakobayashi, Mibu, Shimo-tsuga, Tochigi 321-0293, Japan
Y. Ueda, MD, PhD
Professor and Chairman, Department of Pathology, Koshigaya Hospital, Dokkyo University School of Medicine, 2-1-50 Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan
T. Fujimori, MD, PhD
Professor and Chairman, Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine; Director, Department of Surgical Pathology, Dokkyo University Hospital, 880 Kitakobayashi, Mibu, Shimo-tsuga, Tochigi 321-0293, Japan

The first description of a renal cell carcinoma, in 1883, appears to have been hypernephroma (Grawitz 1883). More recently, investigators have developed a classification system for renal tumors based on cytological appearance, architectural features and presumed cellular origin in the renal tubular system (Colvin 2003; Delahunt and Eble 2002; Kovacs et al. 1997). Recently, a revised pathological classification of kidney tumors has been proposed (Takahashi et al. 2003; Zambrano et al. 1999). Hereditary kidney tumors are associated with genetic disorders, and the same genetic abnormalities are thought to be involved in sporadic kidney cancers (Nagashima et al. 2004).

Herein we describe the World Health Organization (WHO) classification of renal tumors based on pathology (Eble et al. 2004), and discuss relevant issues in arriving at the correct differential diagnosis based on morphological findings.

1.2 Histopathological Classification

Kidney tumors are classified as benign or malignant depending on their histopathological features. Papillary/tubulopapillary adenoma, oncocytic adenoma, and metanephric adenoma are classified as benign. Conventional (clear cell) renal cell carcinoma, papillary renal cell carcinoma, chromophobe renal cell carcinoma, collecting duct carcinoma, cyst-associated renal cell carcinoma, sarcomatoid renal cell carcinoma, and renal medullary carcinoma are classified as malignant (Table 1.1).

Early attempts to develop a classification system of kidney cancers met with limited success (Delahunt and Eble 1998). The first worldwide classification of kidney cancer, the Mainz classification, was based solely on morphological criteria (Thoenes et al. 1986). The WHO has developed a new classification system for kidney cancer based on morphology and molecular findings (Eble et al. 2004).

Table 1.1. Histological classification of kidney tumors. *RCC* renal cell carcinoma

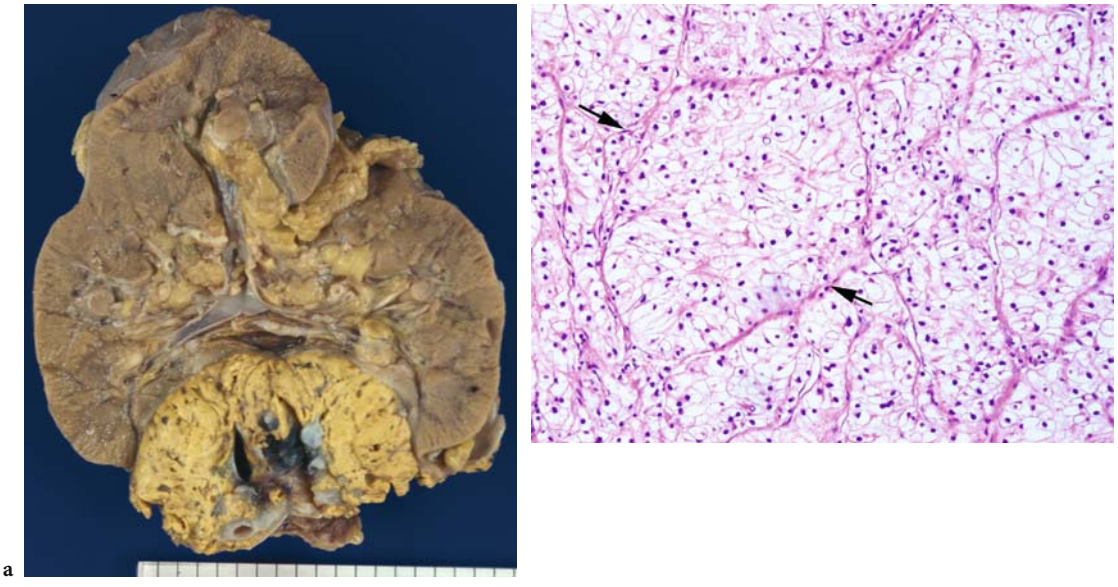
Malignant tumors
Conventional (clear cell) RCC
Papillary renal cell carcinoma
Chromophobe RCC
Collecting duct RCC
Renal cell carcinoma, unclassified
Others: Cyst-associated carcinoma RCC
Sarcomatoid RCC (Spindle RCC)
Granular cell carcinoma
Renal medullary carcinoma
Benign tumors
Papillary/tubulopapillary adenoma
Renal oncocytoma
Metanephric adenoma

1.2.1 Conventional Clear Cell Carcinoma

Renal cell carcinoma (RCC) accounts for 2% of all cancers. Clear cell carcinoma accounts for about 80–90% of all RCC. Generally, patients with RCC are men (by a ratio of 4:1) diagnosed in their sixth decade. Renal cell carcinoma usually presents with micro/macro-hematuria, costal vertebral pain, and abdominal mass (Motzer et al. 1996); however, patients rarely present with this classical triad. Weight loss, anemia, thrombocytosis (Inoue et al. 2004), and abnormal hormone production (Altaffer and Chenault 1979) are common. Renal cell carcinoma may present with hypertension caused by rennin secretion (Hollifield et al. 1975), and polycythemia as the result of erythropoietin secretion (Okabe et al. 1985).

Macroscopic findings of typical clear cell RCC show a rounded, whitish-yellow, sometimes tan-brown or gray, solid, well-circumscribed tumor with focal hemorrhage and necrosis (Fig. 1.1a). A pseudocapsule is often formed by compressed normal parenchyma. Multiple nodules may be present. Cystic change can be marked, and occasionally tumors are seen as small yellow nodules on the inner surface of benign cyst. The size may range from less than 1 cm to more than 25 cm.

Microscopic findings show the usual pattern is predominantly clear cells in an alveolar architecture (Fig. 1.1b). The tumor cells are generally homogenous and characteristically possess clear cytoplasm due to abundant lipid and glycogen (Fig. 1.2). Some of the tumor cells may be eosinophilic or contain granular cytoplasm. Focal dysplastic areas can be seen in adjacent normal tubules. The tumor frequently causes hyalinization and hemorrhage. Immunohistochemically, RCC shows reactivity to keratin (CK8, 18, and 19; Banner et al. 1990; Langner et al. 2004), epithelial membrane antigen (EMA), and vimentin (Waldherr and Schwechheimer 1985). The tumor cells are negative for col-



a **b**

Fig. 1.1a,b. Conventional clear cell carcinoma in a 55-year-old man. **a** Macroscopic view shows a rounded, whitish-yellow, solid, well-circumscribed tumor with focal hemorrhage and necrosis. **b** Microscopic examination shows typical pattern is predominantly proliferation of clear cells, due to abundant lipid and glycogen in an alveolar architecture (*arrows*) (Hematoxylin and eosin stain; original magnification, ×100).

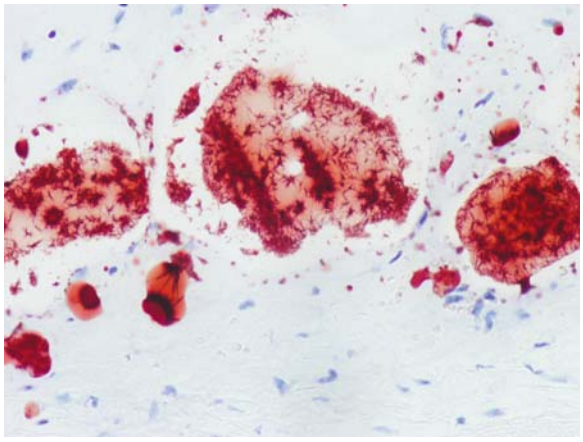


Fig. 1.2. Small conventional clear cell carcinoma in a 42-year-old woman. Microscopic examination shows positive stain for neutral lipid in frozen section (oil red O stain; original magnification, ×200).

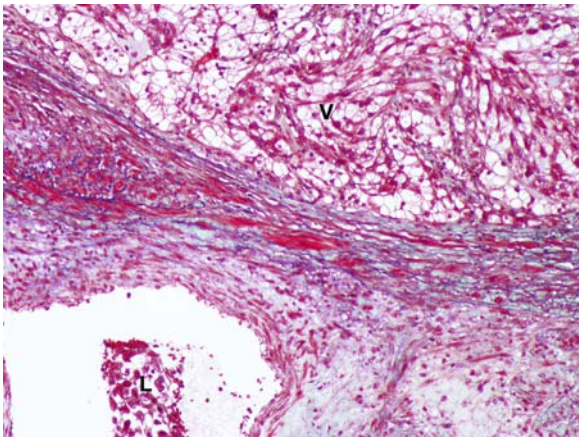


Fig. 1.3. Renal cell carcinoma in a 63-year-old man. Microscopic examination shows that the tumor involves the lymphatic (*L*) and venous (*V*) channels (Elastica Masson stain; original magnification, ×100).

loidal iron, HMB45, and lectin. The tumor tends to invade the renal vein and the inferior vena cava with metastases especially to the lung, bone, liver, and brain (Fig. 1.3; Bukowski et al. 2004).

It is usually not difficult to diagnose clear cell carcinoma, but the possibility of an adrenal rest should be excluded. Distinguishing clear cell carcinoma from adrenal cortical tumor may be difficult; immunohistochemical investigation with CD10 or RCC antigen expression can help. It is important to distinguish between primary and secondary clear cell tumor with vimentin, CD10, and RCC antigen (McGregor et al. 2001).

Prognoses vary depending on tumor size, tumor stage, nuclear grade, DNA content, and proliferation markers. The size of the primary tumor correlates with the likelihood of distant metastases. One rare case of a very small (<3 cm) tumor that had metastasized, as confirmed at autopsy, has been reported (Hellsten et al. 1981). Recently, an increasing number of small renal tumors have been revealed by CT, ultrasound, and MR imaging. Patients diagnosed with renal tumor are classified by tumor stage, with the stage based on surgical material. We use two staging systems: the Robson system is simple and has four stages (Table 1.2; Robson et al. 1967). It is used mainly by urologists. The TNM staging system is more complex but provides more information (Fig. 1.4; Table 1.3; Ficarra et al. 2004; Guinan et al. 1997). It is used by both urologists and pathologists. Tumors can also be graded according to nuclear size, shape, and nucleoli, all of which are considered prognostic factors. The most widely used nuclear grading system is that of Fuhrman et al. (1982; Fig. 1.5; Table 1.4). In the Fuhrman system, there is a distinct prognostic difference between grade-I/II and grade-III/IV tumors. A correlation has been reported between DNA content (ploidy) and nuclear grading. Proliferation markers [Ki-67, nucleolar organizer regions (AgNORs), S-phase fraction, and proliferating cell nuclear antigen (PCNA)] have all been reported to correlate with the prognosis (Srigley et al. 1997).

Table 1.2. Tumor staging system of RCC (Robson criteria)

Stage I	Stage II	Stage III	Stage IV
Tumor confined to the kidney	Perirenal fat involvement but confined to Gerota's fascia	A: Gross renal vein or inferior vena cava involvement	A: Involvement of adjacent organs other than adrenal gland
		B: Lymphatic involvement	B: Distant metastases
		C: Vascular and lymphatic involvement and metastasis to regional lymph nodes	

Table 1.3. The TNM tumor staging system of RCC. (From Guinan et al. 1997)

TNM clinical classification

T: primary tumor

- TX: primary tumor cannot be assessed
- T0: no evidence of primary tumor
- T1: tumor 7.0 cm or less in greatest dimension, limited to the kidney
- T2: tumor more than 7.0 cm in greatest dimension, limited to the kidney
- T3: tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
  - T3a: tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
  - T3b: tumor grossly extends into renal vein(s) or vena cava below diaphragm
  - T3c: tumor grossly extends into vena cava above diaphragm
- T4: tumor invades beyond Gerota's fascia

N: regional lymph nodes

- NX: regional lymph nodes cannot be assessed
- N0: no regional lymph node metastasis
- N1: metastasis in a single regional lymph node
- N2: metastasis in more than one regional lymph node

M: distant metastasis

- MX: distant metastasis cannot be assessed
- M0: no distant metastasis
- M1: distant metastasis

Other classifications

pTNM pathological classification:

pT, pN, and pM categories correspond to the T, N, and M categories

Histopathological grading:

- GX: grade of differentiation cannot be assessed
- G1: well differentiated
- G2: moderately differentiated
- G3–G4: poorly differentiated/undifferentiated

Stage grouping:

- Stage I: T1, N0, M0
- Stage II: T2, N0, M0
- Stage III: T1, N1, M0
T2, N1, M0
T3, N0 or N1, M0
- Stage IV: T3, N0 or N1, M0
Any T, N2, M0
Any T, any N, M1

Table 1.4. Nuclear grading system (Fuhrman grade)

Grade	Size (cm)	Shape of nuclei	Nucleoli
1	10	Round, uniform	Inconspicuous or absent nucleoli
2	15	Slightly irregular	Evident at high power (×400)
3	20	Obviously irregular	Prominent, large at low power (×100)
4	> 20	Bizarre, often multilobed	Heavy chromatin clump

1.2.2 Special Types of Renal Cell Carcinoma

1.2.2.1 Papillary Renal Cell Carcinoma

Papillary RCC is the second most common type of renal tubular tumor in the elderly, accounting for about 10% of all RCC. Papillary RCC is also known as "chromophil RCC" or "tubulopapillary carcinoma." Thoenes et al. (1986) first and Amin et al. (1997) more recently have developed a set of histological criteria for papillary RCC. The male-to-female ratio is 8:1. The prognosis is better than for conventional RCC.

Macroscopic findings of papillary RCC show a rounded, heterogeneous, gray-tan, solid, well-circumscribed tumor with hemorrhage and fibrous capsule (Fig. 1.6a). The tumor size can be less than 20 cm. It is often multiple and bilateral.

Microscopic findings show that papillary RCC is characterized by papillary, tubular, and tubulopapillary growth with several cell patterns over at least 50% of its area (Fig. 1.6b). Thoenes et al. (1986) further divided papillary RCC into eosinophilic, basophilic, and duophilic. Recently, Delahunt and Eble (1997) classified papillary RCC as type 1 or type 2. Type 1 has a papillary pattern of small cells with scant basophilic cytoplasm and low-grade nuclear atypia (grades 1–2). Type 2 is composed of large cells with abundant eosinophilic cytoplasm with large nuclei (grades 3–4). Foamy macrophages and neutrophils are common in the stroma adjacent the tumor. Hemosiderin, glomeruloid papillae, psammoma bodies, edema, and foamy macrophages are common in type 1, but not in type 2. Immunohistochemically, type 1 (80%) and type 2 (20%) tumors show reactivity for Kerain (CK7). Assessment of tumor growth kinet-

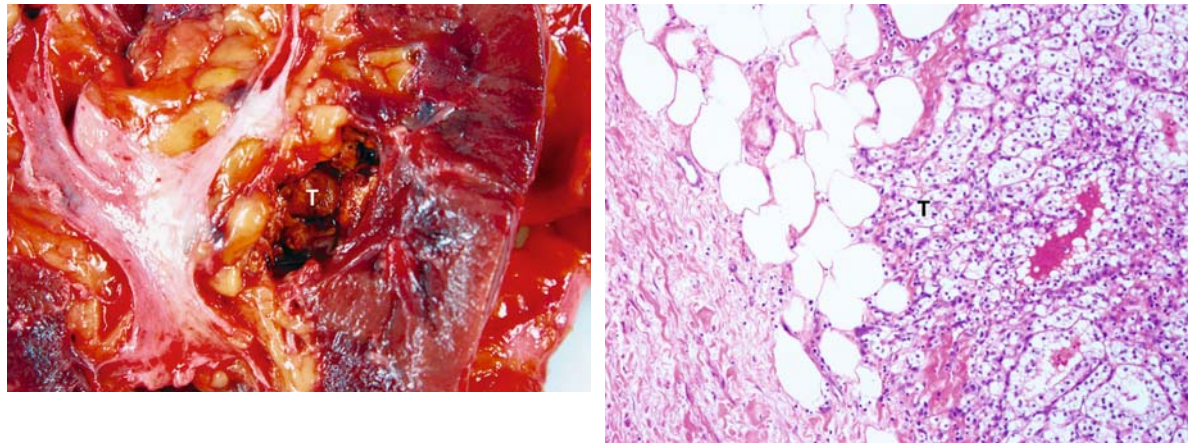


Fig. 1.4a,b. Renal cell carcinoma in a 60-year-old man. **a** Macroscopic view shows the tumor extending into the perinephric tissue (*T*; pT3 tumor). **b** Microscopic examination shows the tumor (*T*) involving the fatty tissue in sinus renalis (hematoxylin and eosin stain; original magnification, ×80).

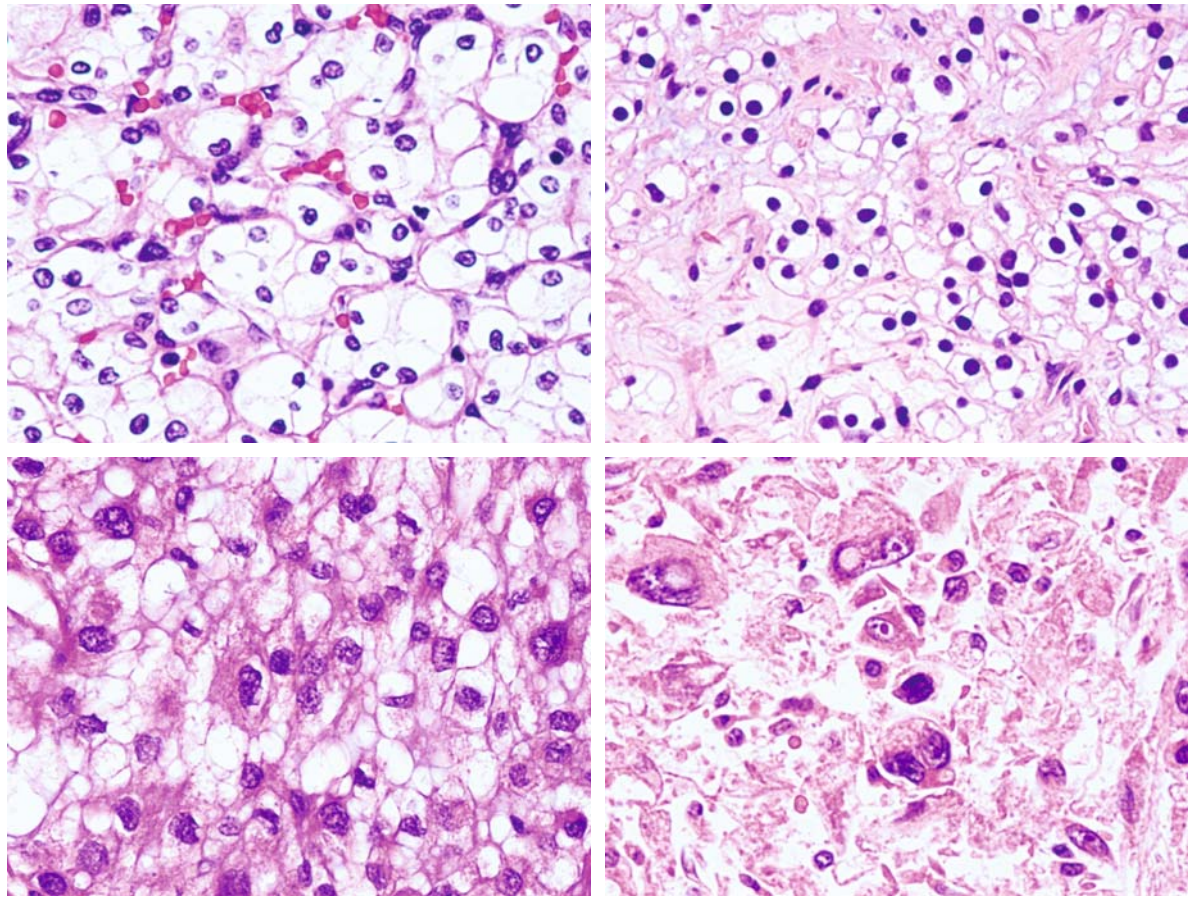


Fig. 1.5a-d. Different grades for renal cell carcinoma by Fuhrman nuclear grading system. **a** Microscopic examination of grade 1 shows the regular, uniform nuclei comparable in size to the red blood cells (hematoxylin and eosin stain; original magnification, ×400). **b** Microscopic examination of grade 2 shows the nuclei varying in size, generally larger than in the grade-1 tumor cells. The chromatins are hyperconcentrated and the nucleoli are frequently visible (hematoxylin and eosin stain; original magnification, ×400). **c** Microscopic examination of grade 3 shows the large nuclei with hyperchromatin along with marked variability in size and shape. The nucleoli are large and conspicuous (hematoxylin and eosin stain; original magnification, ×400). **d** Microscopic examination of grade 4 shows tumor cells exhibiting large pleomorphic nuclei with chromatin clumping and conspicuous nucleoli (hematoxylin and eosin stain; original magnification, ×400).

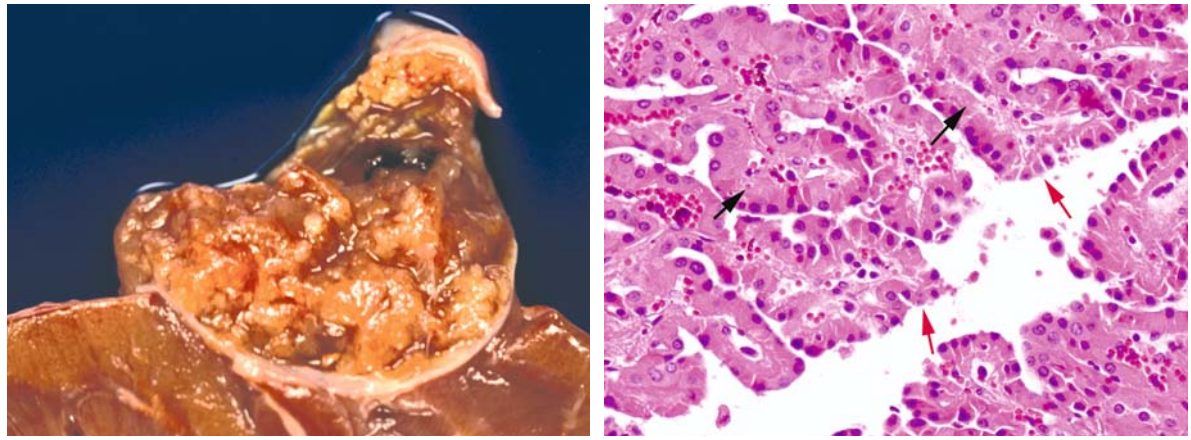


Fig. 1.6a,b. Papillary renal cell carcinoma in a 67-year-old man. **a** Macroscopic view shows a rounded, heterogeneous, gray-tan, solid, well-circumscribed tumor with hemorrhage and fibrous capsule. **b** Microscopic examination shows papillary, tubular, tubulo-papillary growth (*red arrows*) with eosinophilic cells (*black arrows*) (Hematoxylin and eosin stain; original magnification, ×200).

ics showed significant mean AgNOR scores and Ki-67 indices between the two histological types (Delahunt et al. 2001).

It is important to distinguish between benign and malignant renal tumors with papillary projection. Surgical pathologists use a standard protocol to make the distinction: (a) papillary, tubular, or tubulopapillary projection; (b) less than 5 mm in diameter; (c) does not histologically resemble clear cell, chromophobe, or collecting duct RCC (Delahunt and Eble 1997). Collecting duct RCC is stained with lectin-binding protein [*Ulex europaeus* agglutinin-I (UEA-I), anti-keratin MA903] and expresses high molecular weight keratins, but papillary RCC is negative for these markers.

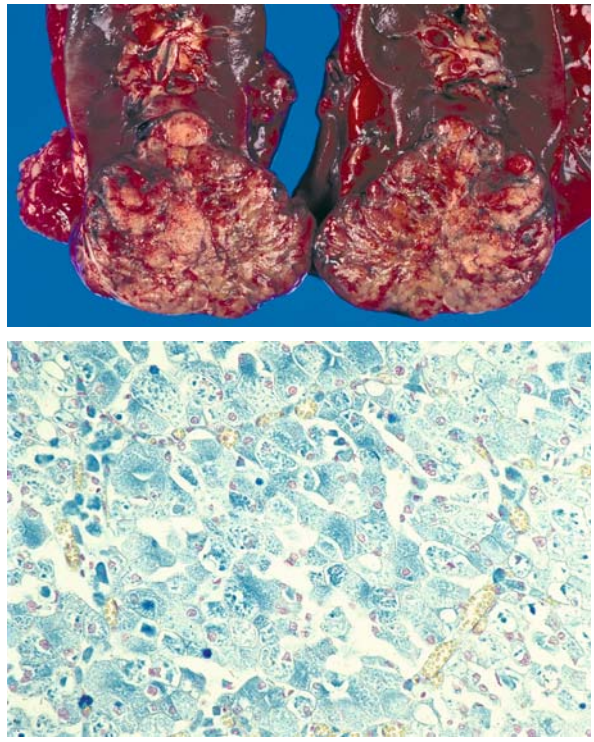
1.2.2.2 Chromophobe Renal Cell Carcinoma

Thoenes et al. first described chromophobe RCC in 12 patients in 1985. It was first recognized in a non-human experimental tumor in 1974 (Bannasch et al. 1974), but it was not established as a variant of human RCC until 2004 (Peyromaure et al. 2004). Chromophobe RCC accounts for less than 6% of renal carcinomas and has a favorable prognosis (Cheville et al. 2003). It affects men and women equally. Chromophobe RCC usually presents symptoms (e.g., abdominal mass) similar to conventional RCC. Immunohistochemical, enzyme histochemical, and ultrastructural findings suggest that the intercalating cells of the collecting duct are the counterpart cells of chromophobe RCC.

Macroscopic findings of chromophobe RCC show a rounded, homogenous, gray-beige, solid, well-circumscribed tumor without hemorrhage or necrosis (Fig. 1.7a). Single nodules may be present. Cystic and hyalinization changes are uncommon. Tumor size may vary. Radiologically, chromophobe RCC tumors are hypovascular, with less prominent vascularity than conventional RCC.

Microscopic findings of chromophobe RCC consist of a solid or glandular growth pattern of large cells with pale/clear cytoplasm called "pale cells" and small cells with eosinophilic cytoplasm called "eosinophilic cells" (Fig. 1.7b). Mixtures of these patterns also occur. The cell membranes are prominent in the solid or glandular pattern (Cochand-Priollet et al. 1997). These cells have little lipid or glycogen compared with conventional RCC. The nuclei are irregular and small, and appear hyperchromatic with a perinuclear halo. Chromophobe RCC usually is lower nuclear grade (grades 1–2). Ultrastructurally, chromophobe RCC commonly reveals numerous micro-cystic vesicles and mitochondria (Thoenes et al. 1985). Immunohistochemically and enzyme histochemically, pale cells and eosinophilic cells stain with colloidal iron (Fig. 1.7c; Thoenes et al. 1985) and show reactivity to keratin (CK18 and CK9; Thoenes et al. 1988), EMA, and paxillin (Kuroda et al. 2001). The tumor cells are negative for vimentin, CD10, and RCC antigen (Avery et al. 2000).

The main differential diagnosis is between oncocytoma and conventional RCC. Colloidal iron stain can distinguish chromophobe RCC from oncocytoma and conventional RCC. CD10, RCC antibody,



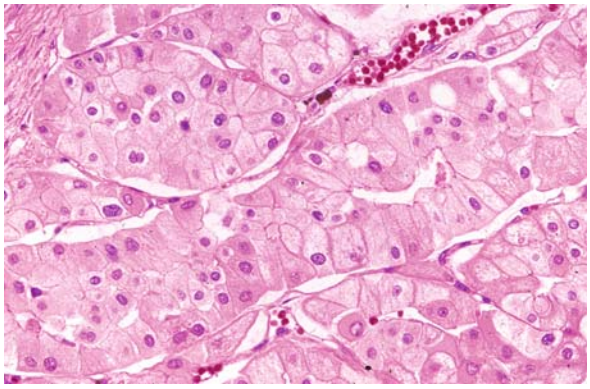


Fig. 1.7a-c. Chromophobe renal cell carcinoma in a 65-year-old man. **a** Macroscopic view shows a rounded, homogenous, gray-beige, solid, well-circumscribed tumor without hemorrhage or necrosis. **b** Microscopic examination shows the solid and glandular growth pattern with "pale cell" and "eosinophilic cell" with perinuclear halo (hematoxylin and eosin stain; original magnification, ×200). **c** Microscopic examination shows positive stain for colloidal iron in cytoplasm (colloidal iron stain; original magnification, ×200).

and vimentin are usually negative, and cytokeratin 18 is expressed in chromophobe RCC. On the other hand, CD10 is positive for conventional RCC, RCC antibody, and negative for vimentin.

1.2.2.3 Collecting Duct Carcinoma

Collecting duct carcinoma, also known as Bellini duct carcinoma, is a rare variant of RCC, representing less than 3% of all malignant renal tumors. The tumor arises from or differentiates from the epithelium of the collecting duct, which is also known as Bellini's duct. In 1976 Mancilla-Jimenez et al. first reported that collecting duct carcinoma is a form of RCC that arises from the collecting ducts. Some pathologists have suggested that collecting duct carcinoma is distinct from other types of RCC.

Collecting duct carcinoma occurs twice as often in men as in women. Initial presentation consists of hematuria and pain. An abdominal mass indicates an advanced metastatic stage (Srigley and Eble 1998). Advanced collecting duct carcinoma may be manifested by fever and leukocytosis caused by tumor-derived inflammatory cytokines (Nagashima et al. 2004). Approximately half of all patients die within 2 years. There is no effective therapy.

Macroscopic findings of collecting duct carcinoma show a solid, white-gray tumor with invasive growth to the renal capsule, spreading to the perirenal fat (Fig. 1.8a). The tumor is usually located in the medulla or central portion of the kidney, and ranges in size from 2.5 to 12 cm. It is often necrotic and shows micro-cystic changes.

Microscopic findings show that collecting duct carcinoma is characterized by papillary, tubulopapillary, cystic, glandular, and solid patterns of tubules with desmoplastic reaction (Fig. 1.8b). Sarcomatoid/spindle cell changes may be present (Kennedy et al. 1990). The tumor cells have a marked nuclear atypia with eosinophilic cytoplasm and a hobnail appearance. Tumor-producing mucin may be identified. A dysplastic epithelium adjacent to the tumor also secretes mucin. These tumor cells are surrounded by desmoplastic and inflammatory stroma with many neutrophils. Immunohistochemically, collecting duct carcinoma shows reactivity to EMA and high molecular weight keratins (CK19, 34betaE12) and stains with lectin [Arachis hypogaea (PNA) and soybean agglutinin (SBA)], UEA-I (Dimopoulos et al. 1993).

Differential diagnosis is sometimes difficult, as macroscopically collecting duct carcinoma resembles papillary RCC. Papillary RCC is positive for lectin-binding proteins from the proximal or distal

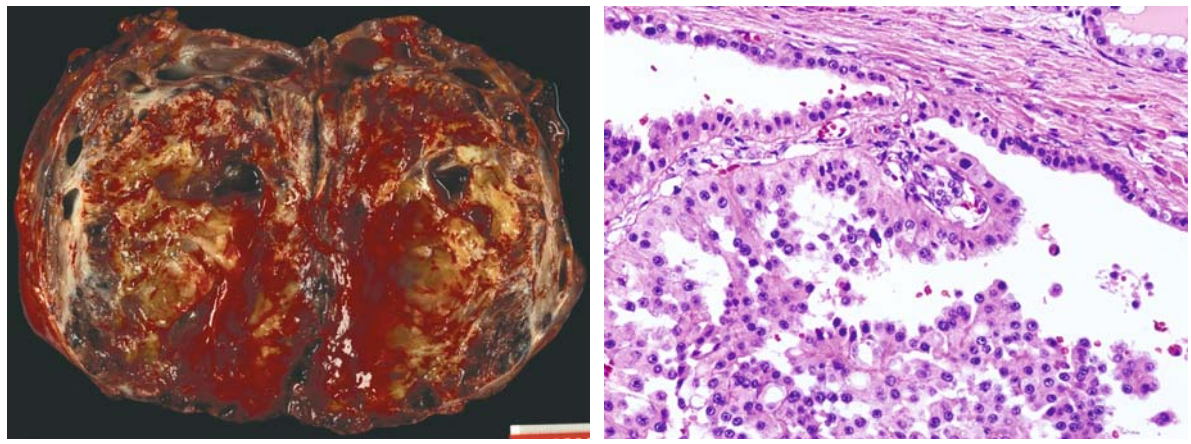


Fig. 1.8a,b. Collecting duct renal cell carcinoma in a 33-year-old woman. **a** Macroscopic view shows a solid tumor with invasive growth to the renal capsule and spread to perirenal tissue. **b** Microscopic examination shows papillary, tubulopapillary, cystic patterns of tubules (hematoxylin and eosin stain; original magnification, ×200).

nephron, but collecting duct carcinoma is positive only for proteins from the distal nephron.

1.2.3 Other Renal Cancers

1.2.3.1 Cyst-Associated Renal Cell Carcinoma

Cyst-associated renal cell carcinoma (also known as multilocular cystic RCC) is an uncommon neoplasm, accounting for only a few rare cases out of all renal tumors (Fig. 1.9a). Perlmann et al. (1928) first described cyst-associated RCC with a lymphangioma containing a small population of clear cells. The tumor appeared to be a distinct subtype of RCC with characteristic gross and microscopic features. Since then, Hartman et al. (1986) have suggested mechanisms by which renal cells may present carcinoma as a cystic lesion. The classification of RCC in Japan lists cyst-associated RCC rather than multilocular cystic RCC. Its etiology and behavior is uncertain, and it may be difficult to distinguish from predominantly cystic neoplasms of the kidney. Histologically, cyst-associated RCC are well-demarcated multicystic lesions containing variably sized aggregates of neoplastic clear cells with low-grade atypia (grade 1). The cyst walls are densely fibrotic and the lining is often devoid of epithelium (Fig. 1.9b). Recently, using immunohistochemistry and lectin histochemistry, it has been demonstrated that cyst-associated RCC originates from the epithelium between the distal convoluted tubule and the collecting duct (Imura et al. 2004). With surgery the prognosis is excellent.

However, there are many patients with long-term hemodialysis in Japan. Long-term hemodialysis frequently causes the renal tubules to dilate, and leads to malignant tumors including RCC associated with acquired cystic kidney disease (Ishikawa 1991). It is also known that RCC occurs as atypical cysts in patients with autosomal-dominant polycystic kidney disease (ADPKD; Fig. 1.10; Keith et al. 1994). It is difficult to distinguish between ADPKD-related RCC and non-related RCC, and diagnosis of ADPKD may require investigation of the patient's family medical history. It has been suggested that an RCC in ADPKD is sarcomatoid change more often than not (Ishikawa and Kovacs 1993).

1.2.3.2 Sarcomatoid Renal Cell Carcinoma

Sarcomatoid RCC was first described by Farrow et al. in 1968 (Fig. 1.11a). These tumors make up less than 5% of all RCC. They have also been known as spindle cell carcinoma, anaplastic carcinoma, or carcinosarcoma. Sarcomatoid RCC is characterized by marked cytological atypia (nuclear grade 4; Fig. 1.11b) and contains enlarged pleomorphic or malignant spindle cells resembling those in sarcoma (Fig. 1.11c–e; Cheville et al. 2004; Peralta-Venturina et al. 2001). The aggressive behavior of sarcomatoid RCC generally leads to a poor prognosis; however, sarcomatoid RCC was not included in a recent classification scheme, because a sarcomatoid component can

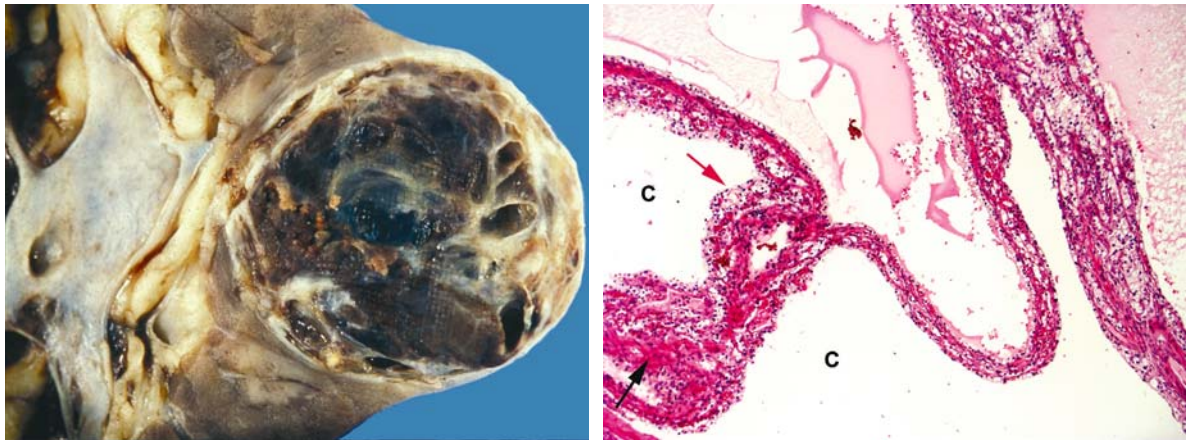


Fig. 1.9a,b. Cyst-associated renal cell carcinoma in a 65-year-old man. **a** Macroscopic view shows a multiloculated tumor with subdividing thin septa into various-sized loculi. **b** Microscopic examination shows multicystic lesions (*C*) containing variably sized aggregates of neoplastic clear cells (*red arrow*) with fibrotic stroma (*black arrow*) (Hematoxylin and eosin stain; original magnification, ×80).

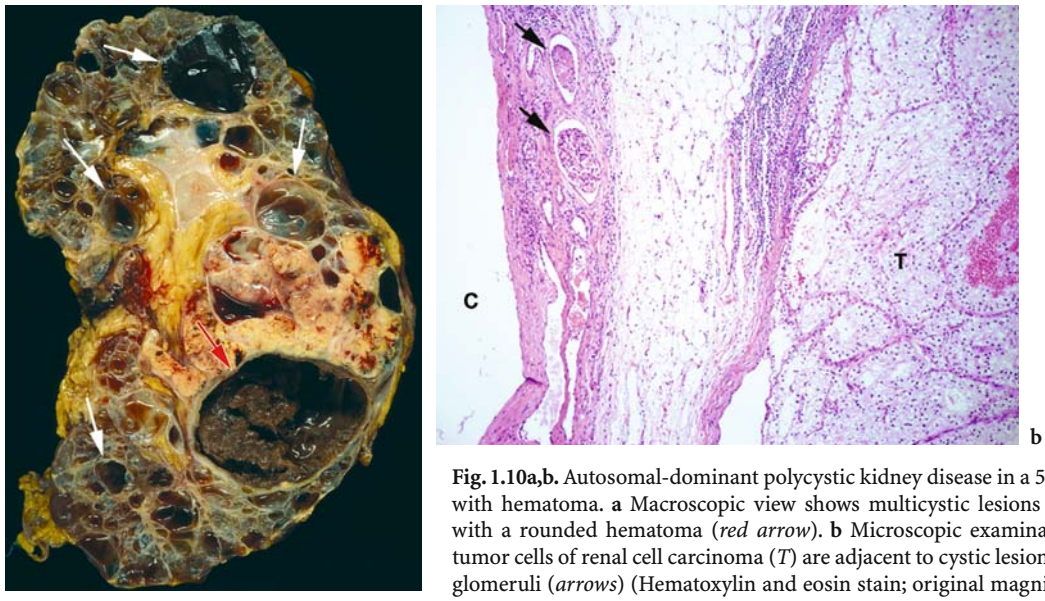


Fig. 1.10a,b. Autosomal-dominant polycystic kidney disease in a 54-year-old man with hematoma. **a** Macroscopic view shows multicystic lesions (*white arrows*) with a rounded hematoma (*red arrow*). **b** Microscopic examination shows the tumor cells of renal cell carcinoma (*T*) are adjacent to cystic lesion (*C*) with intact glomeruli (*arrows*) (Hematoxylin and eosin stain; original magnification, ×80).

occur in all histological subtypes of RCC, especially chromophobe RCC (Akhtar et al. 1997).

1.2.3.3 Granular Renal Cell Carcinoma

Histologically, granular RCC appears granular because of the abundant eosinophilic cytoplasm and mitochondria in its cells. The only point of distinction between granular RCC and conventional RCC is the granular appearance, and distinguishing between granular RCC with low-grade nuclear atypia and benign oncocytoma is difficult. Granular RCC was eliminated from a recently proposed classification (Reuter and Presti 2000), and the term is no longer used in pathological diagnosis.

1.2.3.4 Renal Medullary Carcinoma

In 1995 Davis et al. first described renal medullary carcinoma in conjunction with the sickle cell trait and sickle cell hemoglobin disease. Grossly, tumors range from 4 to 12 cm in diameter and are located in the medulla. Histologically, the tumor resembles a reticular, yolk-sac tumor or an adenoid cystic carcinoma.

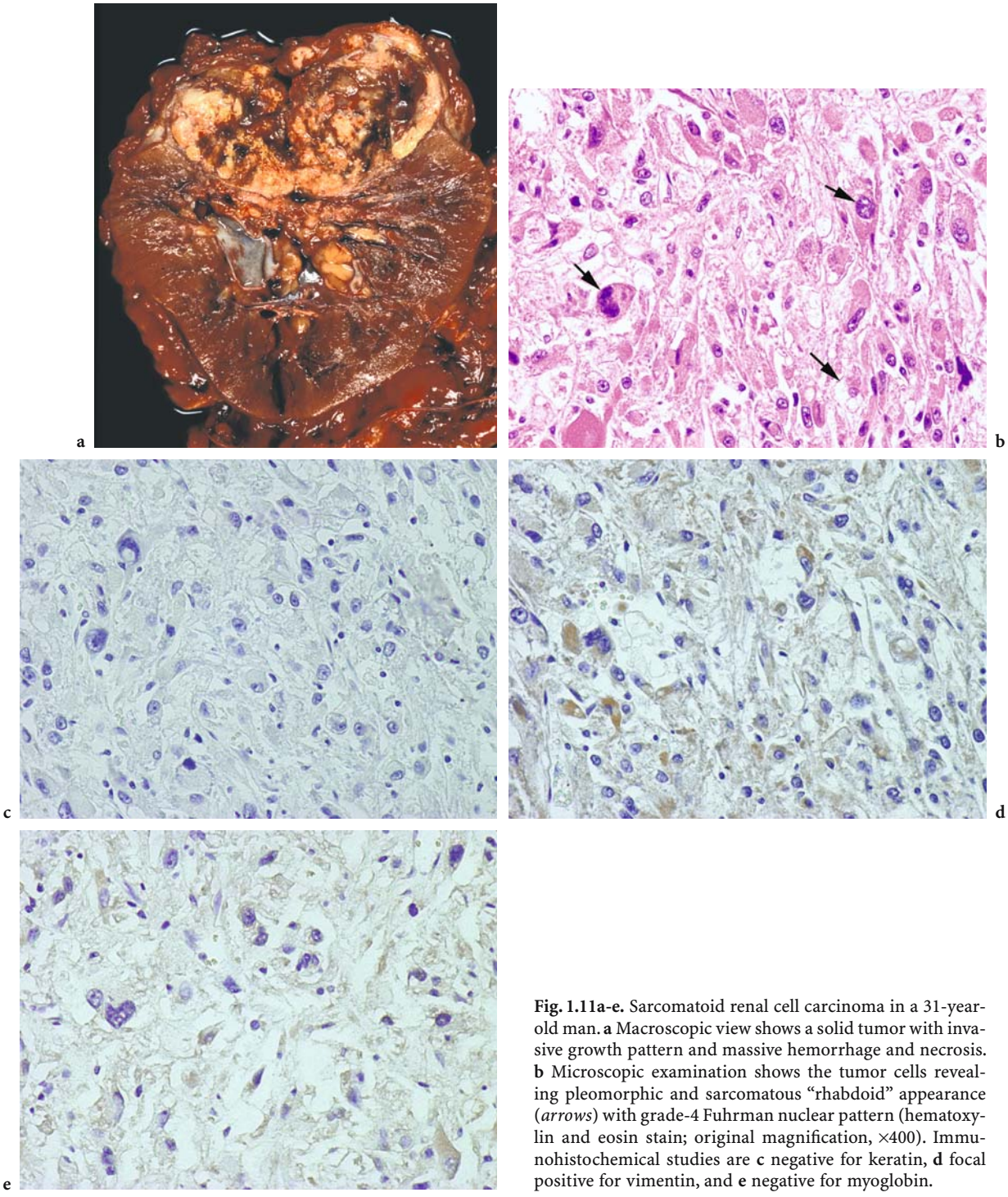


Fig. 1.11a-e. Sarcomatoid renal cell carcinoma in a 31-year-old man. **a** Macroscopic view shows a solid tumor with invasive growth pattern and massive hemorrhage and necrosis. **b** Microscopic examination shows the tumor cells revealing pleomorphic and sarcomatous "rhabdoid" appearance (*arrows*) with grade-4 Fuhrman nuclear pattern (hematoxylin and eosin stain; original magnification, ×400). Immunohistochemical studies are **c** negative for keratin, **d** focal positive for vimentin, and **e** negative for myoglobin.

Peripheral satellites in the cortex and perirenal tissue with venous and lymphatic invasion are common. The tumor has a desmoplastic stroma with inflammatory cells and lymphoid follicles. Its cells react to the same stains as collecting duct carcinoma. The tumor is aggressive (Swartz et al. 2002).

1.3 Cytology

Renal cell carcinoma can be diagnosed with urine cytology. The RCC tumor cells may contain neutral lipids that stain with oil red O or Sudan IV (Fig. 1.12a). The specimen should consist of fresh, unfixed material since lipids dissolve in alcohol. Cytological examination of urine is simple and safe. Urine cytology is primarily for the diagnosis of symptomatic patients. The most common symptom of RCC is gross or micro-hematuria, but voided urine rarely yields adequate material for cytological examination, as tumor cells are not present until an advanced stage (Fig. 1.12b–d). Several investigators have suggested that retrograde catheterization with brush/lavage and fine-needle aspiration biopsy gives better results (Bibbo et al. 1974; Truong et al. 1999).

1.4 Genetic and Molecular Events in Renal Cell Carcinoma

Recent advances in genetic and molecular research have associated some types of RCC with distinct genetic and molecular abnormalities.

The von Hippel-Lindau (VHL) disease is an autosomal-dominant hereditary syndrome. Patients with VHL disease frequently develop conventional RCC (Gnarra et al. 1996). Conventional RCC has a loss of chromosome 3 and loss of function of *VHL* gene mutation (Gnarra et al. 1994). Hypermethylation of the *VHL* gene has been found in conventional RCC (Herman et al. 1994). Abnormalities of the *VHL* gene lead to dysfunction of the hypoxia-inducible factors–VHL protein-elongin B-C (HIF–VBC) complex pathway (Morris et al. 2004). Duplication and trisomy of chromosome 5q (Kovacs 1993) and

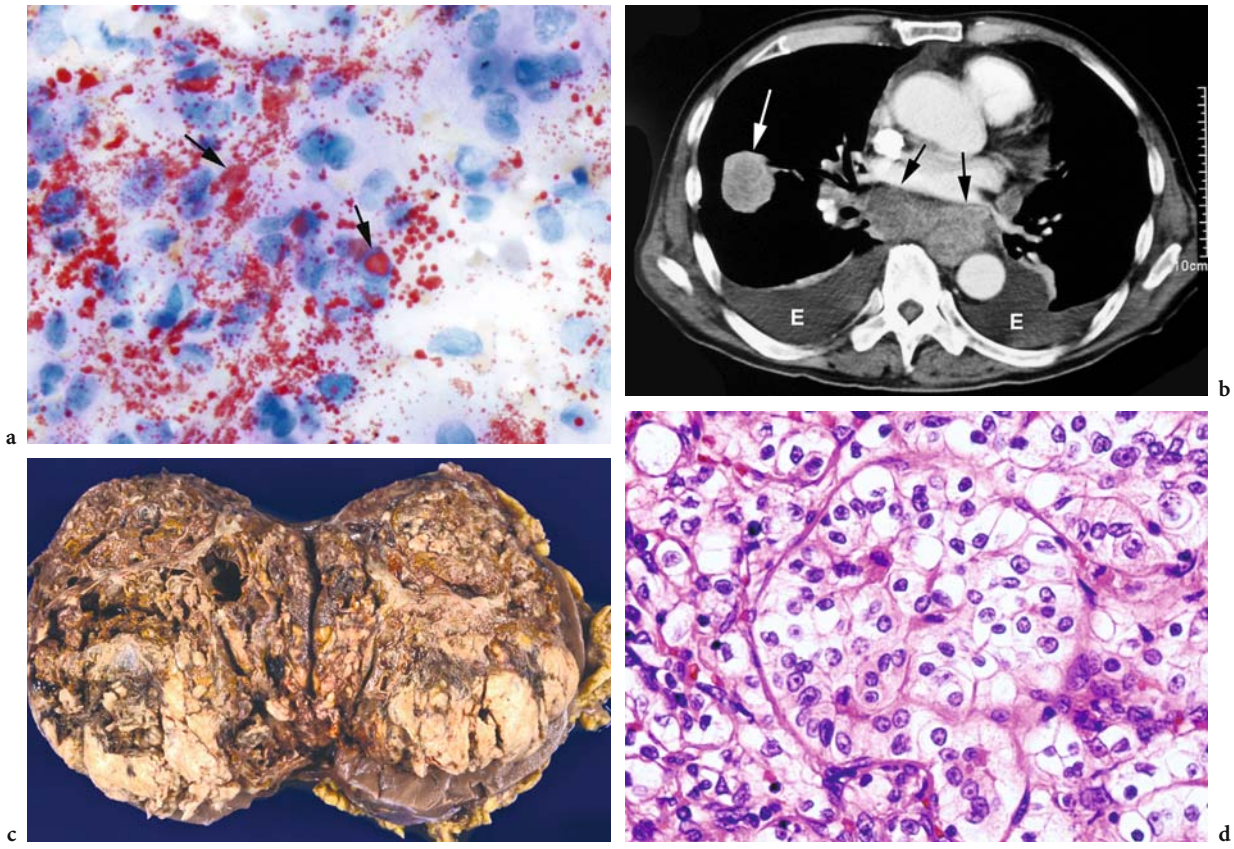


Fig. 1.12a-d. Metastatic renal cell carcinoma in a 63-year-old man. **a** Cytological study shows positive stain (*arrows*) for neutral lipid obtained from pleural effusion (Oil red O stain; original magnification, ×400). **b** Axial contrast-enhanced CT scan shows a large metastasis (*white arrow*) in the right lung associated with a large subcarinal lymph node (*black arrows*) and bilateral pleural effusion (*E*). **c** Macroscopic view of the resected renal neoplasm shows a large, solid tumor with invasive growth to the renal capsule. **d** Microscopic examination shows typical features of renal cell carcinoma consistent with conventional clear cell carcinoma (hematoxylin and eosin stain; original magnification, ×400).

allelic loss of chromosomes 8p, 9p, 11p, 13q, 14q, and 17p (Anglard et al. 1991) have been described in conventional RCC.

On the other hand, papillary RCC has trisomy and tetrasomy of chromosomes 7 and 17 (Bentz et al. 1996). There are gains on chromosome 20 and losses of chromosome 17p and Y chromosome (Dijkhuizen et al. 1996). Translocations between chromosome X and 1 or 17 have been observed in 60–70% of papillary RCC (Heimann et al. 2001; Tonk et al. 1995). Loss of heterozygosity on chromosomes 6p, 9p, 11q, 14q, and 21q (Thrash-Bingham et al. 1995), and the *MET* gene mutations (Schmidt et al. 1997), have been identified in papillary RCC.

Chromophobe RCC carcinoma has a loss of multiple chromosomes and monosomes of chromosomes 1, 2, 6, 10, 13, 17, and 20 (Nagy et al. 2004). Birt-Hogg-Dubé (BHD) syndrome has been characterized by skin tumor, pneumothorax, and renal tumor (Nickerson et al. 2002). This renal tumor was recognized as chromophobe RCC. The *BHD* gene, located in chromosome 1p42, is reported to be a tumor suppressor gene for chromophobe RCC (Okimoto et al. 2004).

Cytogenetically, collecting duct RCC shows a homogeneous chromosome alteration pattern with multiple numerical and structural aberrations (mean 11.1, range 7–15) and continuous involvement of chromosomes 1 and X or Y, both as translocations and deletion/monosomy (Antonelli et al. 2003). Loss of heterozygosity of 1q, 2q, 6p, 8p, 13q, and 21q has been described in this RCC (Fogt et al. 1998).

To our knowledge, there is little genetic and molecular information on renal medullary carcinoma. Recently, Yang et al. (2004) reported the gene expression profiles of two renal medullary carcinomas using micro-arrays containing a 21,632 cyclic DNA clone.

A good genetic and molecular marker of RCC is needed, and several investigators are working to identify markers that can differentiate the subtypes (Boer et al. 2001; Bruder et al. 2004; Lam et al. 2004).

1.5 Conclusion

Management strategies for patients with kidney cancer are progressing significantly, based on advances in basic research and the growing number of clinical trials. Numerous classifications have been proposed, with varying degrees of acceptance, based on morphological and molecular futures; therefore, to arrive at the correct differential diagnosis, it is essential for the pathologist and radiologist to provide effective histological and imaging information to the urologist.

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