Emerging and Recently Described Subtypes of Renal Carcinoma

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Mucinous Tubular and Spindle Cell Carcinoma (MTSCC)

Introduction

Mucinous tubular and spindle cell carcinoma (MTSCC) is an uncommon, low-grade renal epithelial tumor [5, 6]. It was initially believed to derive from the collecting duct and was originally considered the well-differentiated variant of collecting duct carcinoma [6, 7]. This neoplasm has been previously reported under different names: renal cell carcinoma originating from the distal loop of Henle, renal cell carcinoma of distal nephron origin, loopoma, and low-grade collecting duct (Bellini) carcinoma [8]. MTSCC occurs more commonly in females (female-to-male ratio of 2:1 to 3:1) and encompasses a broad age range (17–82 years) [7–9].

Clinical Presentation

Most patients with MTSCC are asymptomatic, although some may experience flank pain and hematuria [5]. A subset of patients may present with renal stones [10]. A common clinical finding is the presence of and associated staghorn renal calculus in approximately 50 % of the cases [5]. MSTCC is often found incidentally when imaging for other indications; however, imaging modalities cannot definitively distinguish MTSCC from other RCC subytes [11, 12]. Reported cases have been found in the subcapsular, corticomedullary, and medullary areas of the kidney, with the majority presenting as clinical stage pT1 [6, 9].

Pathology

On gross evaluation, MTSCC is typically small but can vary in size, is often localized to the cortex or corticomedullary junction, and appears well defined with a tan-white homogenous cut surface [13]. Occasionally, mucin-containing areas may appear gelatinous in nature [5].

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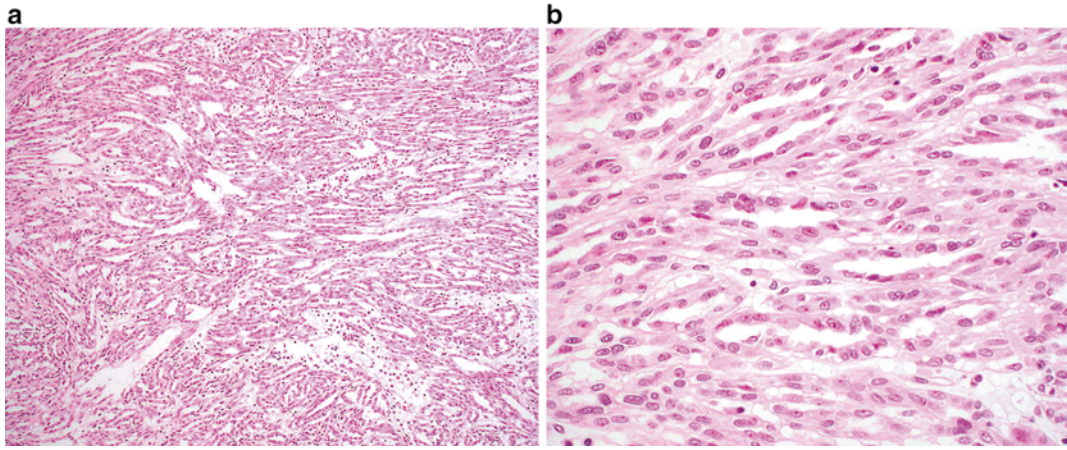

Fig. 9.1 Mucinous and tubular spindle cell carcinoma. (**a**) Inter-anastomosing cords of cells in a mucinous background are seen at low magnification. (**b**) Tumor cells show relatively uniform nuclei with minimal atypia

At low magnification, three distinct components are generally identifiable: a mucinous background, monomorphic spindle cells present in sheets, and cystic, elongated, and compressed tubules lined by a single layer of cuboidal cells (Fig. 9.1a). At higher magnification, the tumor cells are well differentiated and show low-grade morphology and minimal variation in cytologic appearance (Fig. 9.1b). Nuclei are commonly low grade in appearance with a round to oval shape, smooth chromatin, and occasional small nucleoli. The cytoplasm may be eosinophilic, and an admixture of inflammatory cells might be seen [5, 11]. Less common features include papillary architecture, oncocytic change, presence of clear cells, and calcifications (psammoma bodies). Rarely, sarcomatoid change has been described in association with MTSCC [14, 15]. If papillary structures are seen, the main differential diagnosis includes conventional papillary RCC; however, the presence of a mucinous background and the absence of characteristic chromosomal alterations associated with papillary RCC support the diagnosis of MTSCC.

MTSCC has been shown to harbor multiple chromosomal alterations, including 1, 4, 8, 9, 13, 14, 15, and 22 [16]. The genetic changes characteristic of papillary RCC, namely, trisomy 7 and 17 and loss of the Y chromosome, are not identified in MTSCC [17].

Most MTSCC lesions express markers that are reminiscent of distal nephron differentiation, including EMA, AE1/3, CK7, E-cadherin, and α-methylacyl CoA racemase. RCC antigen is positive in the majority of cases. The proximal tubular marker CD10 is positive in only 10–15 % of MTSCC cases [18, 19]. The immunohistochemical profile of MTSCC is nonspecific and partially overlaps with papillary RCC with the absence of CD10 being the most supportive immunohistochemical biomarker for the former [6].

Prognosis and Clinical Management

MTSCC is often indolent and surgery is curative in most cases [20–22]. A small subset of cases may recur or be associated with regional lymph node metastases [13, 16, 22, 23]. Sarcomatoid transformation is associated with an increased likelihood of distant metastases and risk of death from disease [14, 24, 25].

Clear Cell Papillary RCC

Introduction

Clear cell papillary RCC (also referred to by some as “clear cell tubulopapillary RCC”) is reported to

account for less than 5 % of renal epithelial neoplasms; however, this incidence is likely an underestimation due to the misclassification of this tumor as a clear cell or less frequently a papillary, RCC. Clear cell papillary RCC affects men and women equally, and the age distribution ranges from 18 to 88 years [26–28]. Clear cell papillary RCC may occur sporadically or may be associated with end-stage renal disease [29–33].

Clinical Presentation

The majority of clear cell papillary RCC cases are discovered incidentally, although a subset of patients may present with hematuria or flank pain [27].

Pathology

Clear cell papillary RCC is primarily a cortical lesion. On gross evaluation, these tumors are well circumscribed, encapsulated, and relatively small in size (0.6–5.5 cm) [28, 31]. Cystic change may be present. The cut surface ranges from yellow to tan to brown in appearance. These tumors are commonly unifocal, although bilateral and multifocal tumors have been described.

Microscopically, several architectural patterns may be present and include cystic and solid structures as well as branching glands [27, 31, 34]. A defining characteristic of these tumors is the presence of tubular and papillary structures lined by clear cells (Fig. 9.2a). Occasional eosinophilic luminal secretions may be seen. Tumor cells show clear cytoplasm, and the nuclei are uniform and small and lack nucleoli (Fig. 9.2b). Prominent nuclear polarization toward the luminal surface is striking in these cases [27, 31, 35]. The intervening stroma is often fibrous or hyalinized but may contain smooth muscle.

Genetic analysis shows these tumors to be distinct from clear cell RCC and papillary RCC. Specifically, clear cell papillary RCC lacks chromosome 3p deletions or *VHL* gene alteration characteristic of clear cell RCC, as well as extra copies of chromosomes 7 and 17 as is seen in papillary RCC [30, 31, 36–39]. Some molecular differences have been reported between clear cell papillary RCC that occurs in the sporadic and the ESRD settings [31, 40, 41].

Immunohistochemistry is helpful in the diagnosis of this entity by distinguishing it from both clear cell RCC and papillary RCC. Clear cell papillary RCC shows positive immunoreactivity for CK7; carbonic anhydrase IX (CAIX), PAX2, and PAX8; and high-molecular-weight cytokeratin (34βE12) [26, 29, 42]. Immunostains for AMACR (racemase) and RCC antigen are negative, and CD10 is negative or only focally positive. In contrast, clear cell RCC is typically negative for CK7 and positive for CD10, RCC antigen, and CAIX and may show variable AMACR staining. Papillary RCC is typically positive for CK7, AMACR, and CD10; RCC antigen may be variable and CAIX should be negative.

Prognosis and Clinical Management

All cases reported to date in the literature have shown indolent behavior, without recurrence or metastatic spread [1, 32, 33, 42].

Tubulocystic Carcinoma

Introduction

Tubulocystic carcinoma is an uncommon form of RCC described in numerous case reports and small case series [6, 43–46]. Tubulocystic carcinoma was initially described by Amin et al. [43] in 2009; however, earlier descriptions of similar tumors date back to1956, when it was included with Bellini (collecting duct) carcinomas, and later described as the low-grade collecting duct carcinoma [47, 48]. However, more recent studies have demonstrated that tubulocystic carcinomas are more likely related to papillary RCC instead of collecting duct carcinoma [43, 44]. Tubulocystic carcinoma affects adults over a broad age range of 29–94 years of age [49, 50]. There is a strong male predominance (male-to-female ratio of 7:1) [47, 51]. Based on

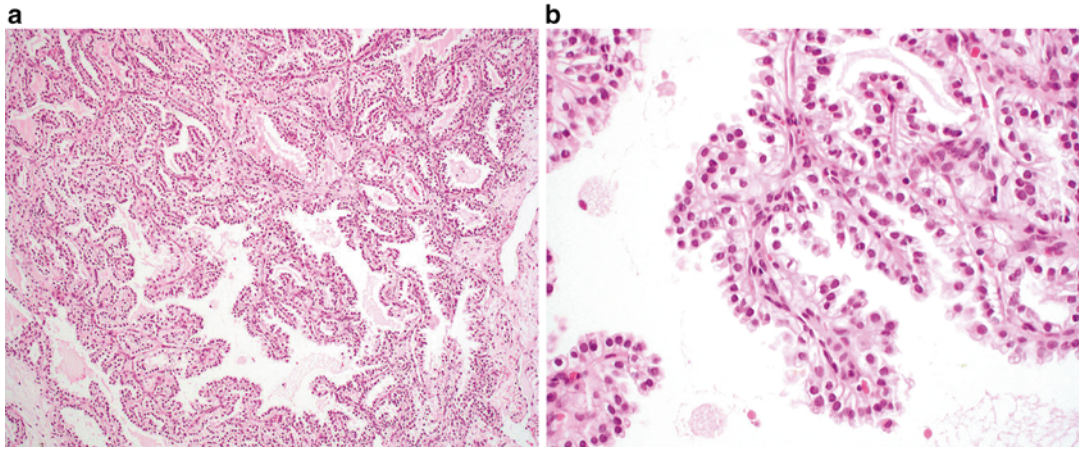

Fig. 9.2 Clear cell papillary renal cell carcinoma. (**a**) A combination of papillary and nested patterns is identifiable in this example. Uniform alignment of the nuclei to the luminal surface is evident even at low magnification. (**b**) Papillary fronds lined by clear cells are a characteristic feature of this lesion

immunohistochemical staining pattern, ultrastructural features, and gene expression profiling, tubulocystic carcinoma is favored to originate from either the proximal convoluted tubule or intercalated tubule [6, 43, 51].

Clinical Presentation

Patients are often asymptomatic, although some may present with abdominal pain, distension, and hematuria. Tubulocystic carcinoma is usually solitary and often involves the left kidney [51]; however, multifocal tumors have been described in approximately 23 % of patients [44, 47]. Tubulocystic carcinoma should be considered in the differential diagnosis of a renal lesion with a cystic component on radiological examination.

Pathology

On gross examination, tubulocystic carcinoma is usually solitary and well circumscribed and has a tan-gray, spongy appearance; the latter is due to numerous cysts/microcysts [47]. Tubulocystic carcinoma varies in size from 0.2 to 17 cm [48, 51]. Multifocal tumors may be present, which can include multiple distinct tubulocystic carcinomas or tubulocystic carcinoma associated with a concurrent second renal neoplasm, most frequently a papillary RCC [47, 48]. Tumors are most commonly located in the cortex, although up to a third can be present at the corticomedullary junction [6].

Microscopically, tubulocystic carcinoma is composed of many cystic structures that are small to medium in size, which are separated by thin fibrous septa (Fig. 9.3a). Solid growth is not seen. The cells lining the cysts are cuboidal, columnar, or hobnail in appearance with abundant eosinophilic or amphophilic cytoplasm which characteristically contain large nuclei with prominent red nucleoli (Fig. 9.3b) [47]. Rarely, sarcomatoid features may be seen in association with this tumor but only in the presence of solid growth (i.e., an associated component of high-grade papillary RCC) [1, 52]. On ultrastructural examination, the tumors show abundant microvilli with brush border organization suggestive of proximal convoluted tubules, with some features resembling intercalated cells of the collecting ducts [51].

Genetic analysis of these tumors report a similar profile to papillary RCC, which include gains of chromosome 7 and 17 and loss of the Y chromosome. However, classic features associated with "low-grade" papillary RCC are typically not

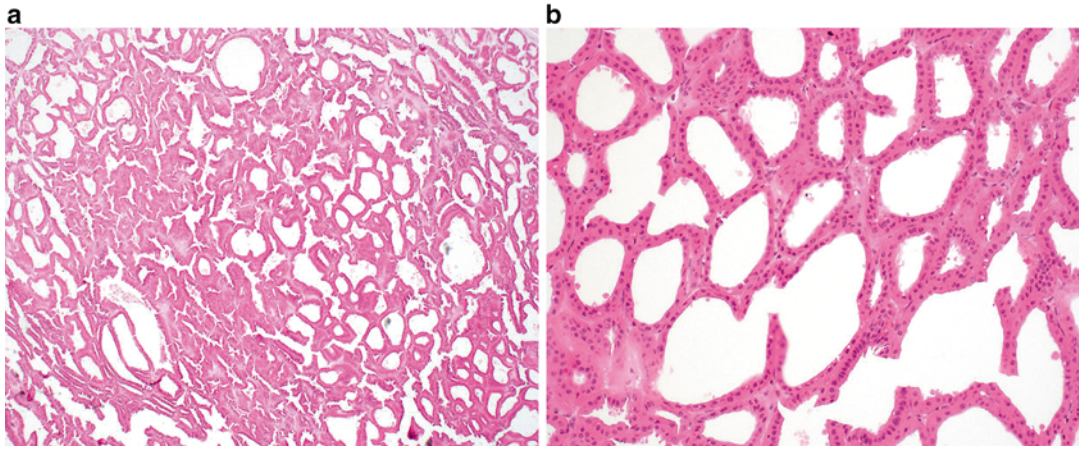

Fig. 9.3 Tubulocystic renal cell carcinoma. (**a**) Multiple cystic structures of variable size are present at low magnification. (**b**) Cysts are lined by a single layer of cells with eosinophilic cytoplasm, large nuclei, and prominent nucleoli

seen in this entity; in contrast, high-grade tumors with solid and papillary growth patterns and similar nuclear and immunophenotypic features can be seen [44, 45, 53]

Immunohistochemical studies demonstrate immunoreactivity for cytokeratins 8, 18, and 19 [6, 44]. CD10 and P504S (racemase) are positive in greater than 90 % of cases. Diffuse and strong AMACR positivity, positive to variable CK7 expression, and staining for kidney-specific cadherin and PAX2 have been reported [44, 47]. Tubulocystic carcinoma is negative for high-molecular-weight cytokeratin (34BE12) [47, 48].

The main differential diagnoses include other tumors with a multiloculated gross appearance, including multiloculated clear cell RCC, cystic clear cell tubulopapillary RCC, cystic nephroma, mixed epithelial and stromal tumor, and cystic oncocytoma [47, 51, 54, 55]. Distinction between these entities is primarily based on light microscopic evaluation, rather than use of ancillary studies.

Prognosis and Clinical Management

Whereas the majority of reported cases of tubulocystic carcinoma demonstrate indolent behavior, recurrence and metastases to regional and distant sites such as the bone and liver have been reported in rare cases; the latter is associated with tumors that demonstrate solid and papillary growth patterns [44, 45, 47, 51, 56].

Acquired Cystic Disease-Associated RCC

Introduction

Cystic change occurs in the majority of patients with end-stage renal disease (ESRD) who undergo dialysis and is termed "acquired renal cystic disease" (ARCD) [5, 6]. Patients with ARCD have increased risk of developing RCC comparing to normal population [6, 57, 58], with an RCC incidence rate of 10 % in ARCD patients [5, 6, 37, 59]. A direct correlation between the duration of dialysis and RCC development in ESRD patients has been suggested in some studies [5, 6, 29, 60]. Multiple types of renal neoplasms may arise in the background of ESRD, including clear cell RCC, papillary RCC, clear cell papillary RCC, and chromophobe RCC [5, 61–63], although acquired cystic disease-associated RCC represents up to 36 % of all renal neoplasms in this setting [29]. Similar to non-ESRD RCC, acquired cystic disease-associated RCC occurs most commonly in men between the ages of 55 and 65 years [5, 30, 40, 61].

Clinical Presentation

Most cases are found as an incidental finding on nephrectomy specimens removed for ESRD [5]. However, a subset of patients undergoing dialysis may have pain or demonstrate hematuria. In addition, imaging may identify an incidental lesion in the background of cystic renal parenchyma [6, 62].

Pathology

On gross examination, acquired cystic disease-associated RCC is well circumscribed and tan/yellow in appearance and may show focal hemorrhage or necrosis [5, 6]. The background renal parenchyma shows multiple variably sized cysts, with the neoplasm appearing to arise in association with a cyst wall or from one of the connecting trabecular areas. Multifocal tumors occur approximately 50 % of cases, and bilateral tumors are found in up to 20 % of patients [1, 29].

At low magnification, acquired cystic disease-associated RCC shows a distinct "sieve-like" appearance (Fig. 9.4a). At higher magnification, multiple growth patterns that include acinar, alveolar, solid, cystic, and papillary regions may be identified. The tumor cells show granular, eosinophilic cytoplasm and contain large nuclei with prominent nucleoli [6]. Intratumoral calcium oxalate crystal is a relatively specific feature in this entity, although may be lacking a minority of cases (Fig. 9.4b) [6, 29, 59]. Rhabdoid and sarcomatoid features have been reported in a small number of cases [29, 61, 64].

Fluorescence in situ hybridization (FISH) and comparative genomic hybridization performed on nine cases showed variable combined gains of chromosomes 3, 7, 16, 17, and Y [6, 60].

Acquired cystic disease-associated RCC shows immunoreactivity for a-methylacyl-coenzyme A racemase (AMACR), CD10, RCC antigen, and glutathione S-transferase A [6, 60]. CK7 is often negative but can show focal immunoreactivity [6].

The main differential diagnosis includes papillary renal cell carcinoma. Immunostains for CK7 and chromosomal analysis can be used to distinguish these two entities in most cases, if required.

Prognosis and Clinical Management

Most cases of acquired cystic renal disease-associated RCC typically show indolent behavior, which may reflect early detection in patients with ESRD [6, 62]. As anticipated, the minority of tumors that show rhabdoid or sarcomatoid features may behave more aggressively and be associated with metastatic spread [1, 29, 64, 65].

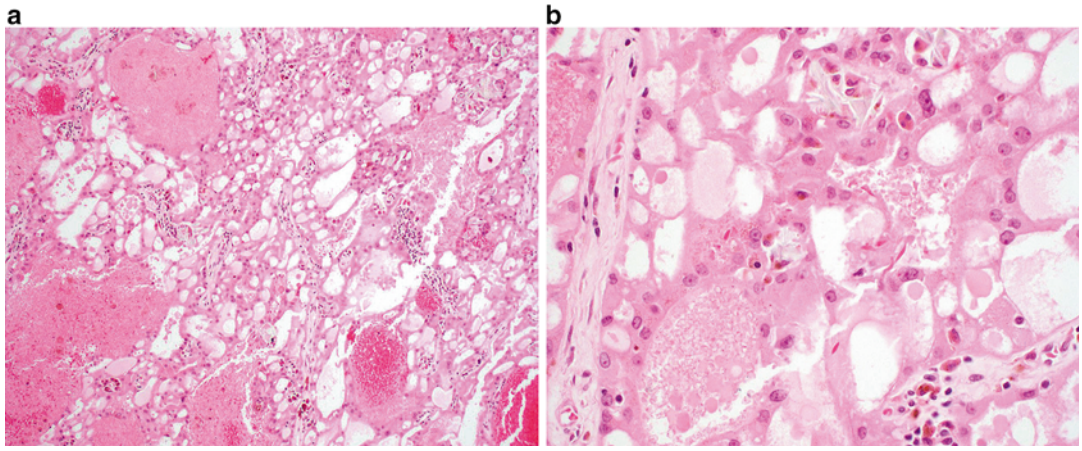

Fig. 9.4 Acquired cystic disease-associated renal cell carcinoma. (**a**) A sieve-like pattern is evident at low magnification. (**b**) Crystals may be seen in a subset of cases

Neuroblastoma-Associated RCC

Introduction

Neuroblastoma-associated RCC is a unique entity that occurs 3–35 years after diagnosis and treatment of childhood or adult neuroblastoma [5, 6, 66, 67]. It is a rare tumor, accounting for less than 1 % of all cases of RCC and approximately 2.5 % of the cases of RCC in children [5, 11]. Males and females have an equal risk of involvement [63]. Some reports suggest a relationship between the treatment for neuroblastoma and development of neuroblastoma-associated RCC [11]. However, a small number of patients develop RCC in the absence of radiation or chemotherapy, suggesting a possible underlying germ line susceptibility for these lesions [67].

Clinical Presentation

Neuroblastoma-associated RCC can be unilateral or bilateral [11]. Rare cases showing multifocal tumors have also been reported. No specific radiologic findings have been associated with this entity. The diagnosis may be suggested based on a history of treatment for neuroblastoma [11].

Pathology

On gross evaluation, tumors range in size from 1 to 8 cm [5, 63]. Neuroblastoma-associated RCC is histologically heterogeneous [11]. The most common appearance is that of an oncocytic tumor that shows solid and papillary architecture and occasional vacuolization of the cytoplasm [5, 53, 63, 68]. Variable nuclear size and medium-sized nucleoli are present, and mitotic figures may be identified. One should note that other forms of RCC, including Xp11.2 translocation-associated carcinoma and classic clear cell RCC, can also occur in a subset of patients following neuroblastoma [5, 63, 69].

Due to the small number of cases described to date, the genetic profile of this tumor has not been well defined, although chromosomal alterations affecting 14q31 and 20q13 have been reported [5, 70].

Immunohistochemistry shows neuroblastoma-associated RCC to be frequently positive for EMA, vimentin, and cytokeratins 8, 18, and 20 and negative for cytokeratins 7, 14, 19, 20, S100, and HMB45 [5, 63]. The main differential diagnosis includes oncocytoma and chromophobe RCC in the oncocytic subtype of neuroblastoma-associated RCC. Clinical history is critical in this differential diagnosis.

Prognosis and Clinical Management

The oncocytic subtype of neuroblastoma-associated RCC behaves in an indolent manner. Outcomes associated with clear cell RCC and Xp11-associated RCC are likely similar to their de novo counterparts. Awareness of this entity is important to ensure close follow-up and frequent assessment of survivors of neuroblastoma in order to detect RCC early in the course of disease.

Thyroid-Like Follicular Carcinoma of the Kidney (TLFCK)

Introduction

Thyroid-like follicular carcinoma of the kidney (TLFCK) is a rare renal neoplasm. To date, only a limited number of TLFCK cases have been reported in the literature [1, 6, 71–75]. This tumor occurs over a broad range of 29–83 years, with an equal gender distribution [1, 6, 73, 75]. This entity has not yet been classified as a distinct renal neoplasm by the World Health Organization.

Clinical Presentation

Most of these carcinomas are identified as an incidental finding on radiologic imaging, although a subset of patients present with abdominal pain, flank pain, hematuria, and relapsing urinary infection [6, 71, 75].

Pathology

On gross examination, these tumors are well defined and encapsulated, with a solid or cystic and yellow-tan cut surface [71, 75]. Focal areas of hemorrhage or necrosis may be seen. Microscopically, TLFCK shows variably sized follicular structures containing both microfollicular and macrofollicular patterns (Fig. 9.5a). The follicles contain pink colloid-like material and are lined by a single layer of cuboidal to columnar cells with moderate amphophilic to eosinophilic cytoplasm (Fig. 9.5b) [71, 73]. Nuclei are typically round to oval and may demonstrate nuclear grooves, similar to that seen in thyroid neoplasms. Lymphocytic infiltrates with or without reactive germinal centers can be present [71].

Given the low incidence, the genetic profile of TLFCK has not been well defined.

The immunohistochemical profile of TLFCK shows positive immunoreactivity for PAX8, EMA, CK7, and vimentin, with a subset of cases reported to express CD10 and PAX2 [71, 76]. The colloid-like material in TLFCK is composed of Tamm-Horsfall glycoprotein, the most abundant protein in normal urine [71, 77]. The main differential diagnosis is metastatic follicular carcinoma of the thyroid; however, TLFCK is negative for thyroid markers TTF-1 and thyroglobulin [6, 71]. The diagnosis of TLFCK is strengthened by the absence of lesions in the thyroid or other locations by imaging [6, 73]. TLFCK should also be distinguished from thyroidization of the kidney, which is characterized by atrophic distal tubules or collecting ducts, with colloid-like hyaline casts that mimic normal thyroid parenchyma. Thyroidization is a benign, widespread, and usually bilateral process that occurs in patients with a history of chronic pyelonephritis, obstructive uropathy, or end-stage renal disease. In contrast, TLFCK presents as a well-circumscribed tumor in a background of unremarkable kidney and is often in patients with no history of renal disease [71].

Prognosis and Clinical Management

Although most cases of TLFCK remain localized, one case of TLFCK metastasized to the renal hilar lymph nodes and a second showed widespread metastases to the lungs and retroperitoneal lymph nodes [71, 73].

Succinate Dehydrogenase-Deficient RCC

Introduction

Succinate dehydrogenase (SDH)-deficient renal cell carcinoma is a recently described entity that is not yet widely recognized due to its morphologic

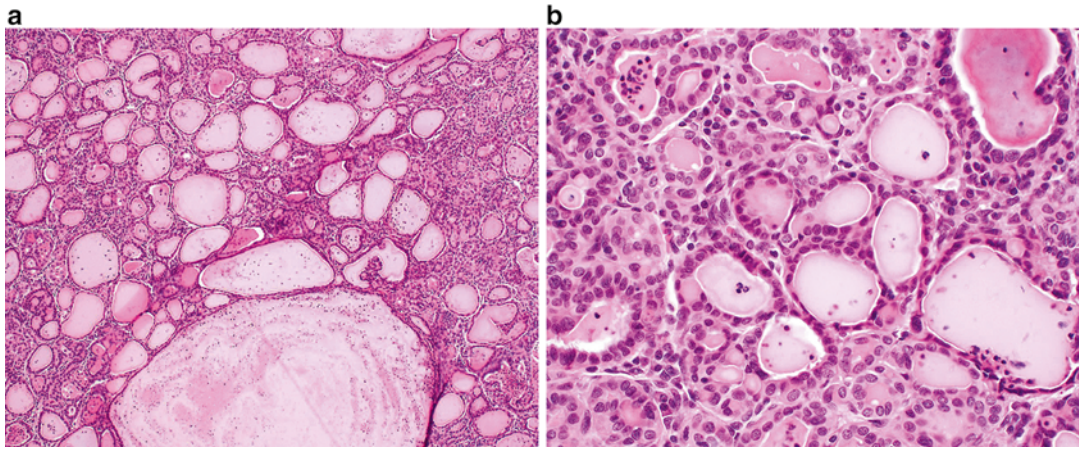

Fig. 9.5 Thyroid-like follicular carcinoma of the kidney. (**a**) A combination of variably sized follicular structures filled with colloid-like material and small nests may be seen in this entity. (**b**) The follicular structures are lined by a single layer of cuboidal to columnar cells with eosinophilic cytoplasm and minimal nuclear atypia

overlap with other oncocytic renal neoplasms. Nevertheless, SDH-deficient RCC has been accepted as a provisional entity in the 2013 International Society of Urological Pathology Vancouver Classification of renal tumors, as it represents a distinct renal neoplasm, defined by loss of IHC staining for the B subunit of the SDH mitochondrial complex (the entire complex consists of four subunits: A, B, C, and D) [1, 78, 79]. The tumor is rare, estimated as less than 1 % of all renal epithelial tumors [79], and it occurs in individuals with germ line mutations of the genes that encode the SDH complex [1, 78]. SDH-deficient RCC has been reported more commonly in men, with the mean age of 40 years [78, 79]. Patients with germ line mutation in a SDH subunit gene are also prone to develop paraganglioma/pheochromocytoma, gastrointestinal stromal tumor (GIST), and pituitary adenoma [1, 78–80].

Clinical Presentation

Due to the low incidence of this renal cancer, clinical presentation has yet not been described in detail. Some patients have reported episodic headache and palpitation associated with paraganglioma-related hypertension, with an incidental renal mass discovered on imaging during work-up [81]. Bilateral tumors have been reported [79].

Pathology

On gross examination, this tumor is well circumscribed with a tan to red cut surface [78, 79]. Hemorrhage and microcystic change may be present [78, 79]. Tumor diameter ranges from 2.0 to 20 cm [78]. Both unifocal, multifocal, and bilateral tumors have been described [78, 79].

Microscopically, cells are arranged in solid or nested patterns that contain uniform neoplastic cells with eosinophilic, variably granular cytoplasm [1, 78, 79, 81]. The most distinctive histological feature is the presence of perinuclear cytoplasmic vacuoles and inclusion-like spaces, some of which contain pink flocculent-like material (Fig. 9.6) [78, 79, 81]. Nuclei are typically round with smooth boarders, finely clumped chromatin, and small or inconspicuous nucleoli [78]. Benign tubules or glomeruli are often entrapped at the edges of the tumors [81]. Stromal hemorrhage, fibrosis, and hyalinization are commonly seen [78]. Intratumoral mast cells and aggregates of lymphocytes, as well as necrosis, may be present [78]. Sarcomatoid change has been described [79].

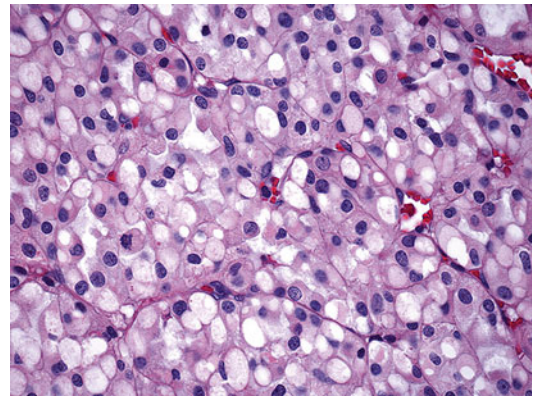

Fig. 9.6 SDHB-associated renal cell carcinoma. Distinctive features include perinuclear cytoplasmic vacuoles and inclusion-like spaces filled with *pink secretions*

By immunohistochemistry, the characteristic and pathognomonic finding is loss of SDHB; however, this can occur when any of the four SDH complex components (A, B, C, or D) are mutated. In SDHB-mutated RCC, the SDHA antibody will highlight the perinuclear cytoplasmic inclusions which contain the mutated mitochondria [78, 79]. Immunohistochemistry beyond loss of expression with SDH antibodies is nonspecific: neoplastic cells are positive for PAX8 (confirming renal origin), EMA, and S100 and negative for RCC; labeling for CAM5.2, AE1/AE3, cytokeratin 7, CD10, and AMCR is variable, and C-KIT highlights intratumoral mast cells but is negative in the tumor cells [78, 79].

The differential diagnosis of SDH-deficient RCC includes oncocytoma, chromophobe RCC, and the "granular variant" of clear cell RCC. Loss of staining for SDHB is a definitive confirmation of the diagnosis. Also, SDH-deficient RCC commonly shows negative or focal cytokeratin reactivity [79].

Prognosis and Clinical Management

Metastatic disease to the liver, lung, ribs, vertebrae, adrenal gland, and lymph nodes has been reported. Concurrent paragangliomas may also be observed [78, 79, 81]. Tumor progression and death from disease have been reported [78, 79, 81].

TCEB1-Mutated (Monosomy-8) Renal Cell Carcinoma

Renal cell tumor with TCEB1 mutations and loss of heterozygosity of chromosome 8 are a recently described renal tumor variant that has morphologic overlap with clear cell RCC and clear cell papillary RCC [82, 83]. This emerging renal neoplasm was identified through common mutations in the TCEB1 gene (which encodes elongin, a member of the VHL complex) and by loss of chromosome 8 with conventional G-band karyotyping and fluorescence in situ hybridization. To date, only 17 tumors have been reported [82–84]. Alterations of TCEB1 impact VHL-pathway signaling, a commonly altered pathway in clear cell renal cell carcinoma, but in a mechanism that is independent of direct VHL mutation [82, 84].

Clinical Presentation

All but one reported TCEB1-mutated RCCs reported to date have been small (stage pT1) and therefore likely to present incidentally, although nonspecific symptoms typically associated with other renal masses (pain and hematuria) may be present.

Pathology

Grossly, tumors are typically small, tan/yellow, and well circumscribed. A prominent thick fibrous capsule is almost invariably present. Microscopically, TCEB1-mutated tumors show nests and tubule of clear cells with occasional focal papillary structures. Cells contain abundant clear cytoplasm and pink amorphous material within tubule lumens [82, 83] (Fig. 9.7a). Nuclei are low grade but typically larger than is seen in clear cell tubulopapillary RCC; nucleoli are absent (i.e., size suggestive of Fuhrman nuclear grades 2–3, but absence of nucleoli is more in keeping with Fuhrman nuclear grade 2). There is a hint of nuclear polarization but not to the extent seen in clear cell papillary RCC. A relatively distinct and reproducible feature is the presence of thick fibromuscular bands that dissect through the mass (Fig. 9.7b).

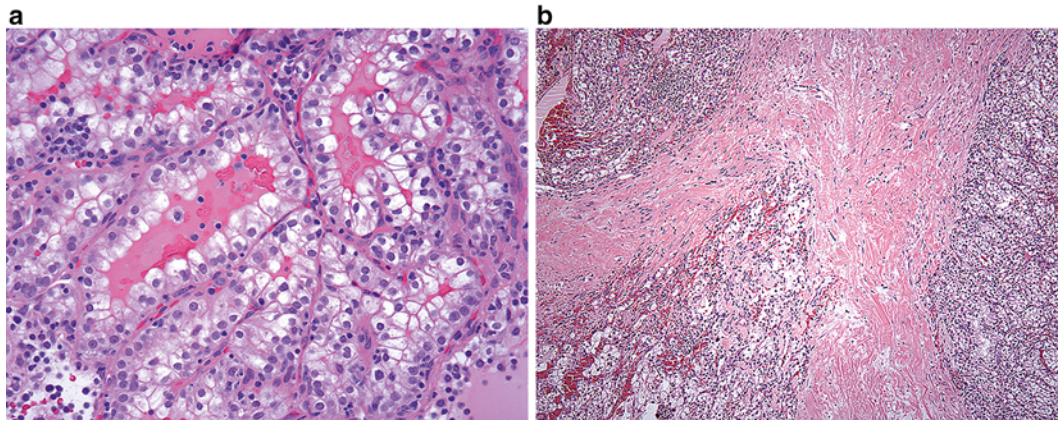

Fig. 9.7 TCEB1-mutated renal cell carcinoma. (**a**) Tubular structures lined by clear cells with abundant clear cytoplasm. *Pink amorphous material* is present in the tubule lumen. (**b**) A unique feature is the presence of thick fibromuscular bands within the lesion

Immunohistochemistry shows immunoreactivity for CAIX and HIF-1-alpha, as well as CK-7; the latter distinguishes it from most clear cell RCCs. Tumor cells are negative for high-molecular-weight cytokeratin (34BE12) [82], and unlike clear cell tubulopapillary RCC, TCEB1-mutated tumors show variable staining for AMACR, CD-10, and RCC antigen [83]. Of note, the cuplike staining pattern described for CAIX in clear cell papillary RCC is not present in TCEB1-mutated RCC; instead a membranous pattern, similar to clear cell RCC, is observed.

The differential diagnosis includes both clear cell renal cell carcinoma and clear cell papillary renal cell carcinoma. Although morphological features can be very suggestive and immunohistochemistry can be supportive, definitive diagnosis requires molecular analysis to show mutations in the TCEB1 gene and/or loss of heterozygosity at the chromosomal region that contains TCEB1 (8q21.11). Clinically, the use of G-band karyotyping (fresh tissue required) or FISH analysis (possible with formalin-fixed tissue) can be used to demonstrate a loss of chromosome 8. The short arms of chromosome 3 should be intact to make a diagnosis of a TCEB1-mutated RCC.

Prognosis and Clinical Management

All cases reported thus far have been low stage (pT1), except one pT3a case. During a median 48-month follow-up period, no patient was reported to develop metastatic disease. However, further evaluation on a larger number of tumors with extended follow-up is needed to determine outcomes relative to conventional clear cell RCC.

Renal Carcinoid Tumor

Introduction

Less than 1 % of carcinoid tumors arise in the genitourinary system, with the testes and ovaries being the most common locations, followed by the kidneys [85]. Primary renal carcinoid tumor of the kidney is very rare, and less than 100 cases are reported in the literature [5, 86]. Age of diagnosis is broad, ranging from 13 to 79 years [86, 87]. There is an equal male-to-female distribution [5]. Intrinsic neuroendocrine cells in normal kidneys have not been reported previously; however, the pathogenesis of renal carcinoid tumors is controversial [86]. Carcinoid tumors in the kidney have been suggested to occur in patients with underlying renal congenital or acquired anomalies such as horseshoe kidney and mature teratoma [86, 88, 89]. These tumors demonstrate distinct morphological features from small cell carcinoma, which have also been reported to occur in pure form in the renal cortex [90, 91] or associated with invasive urothelial carcinoma of the renal pelvis [92].

Clinical Presentation

Patients may present with abdominal pain or fullness, gross hematuria, and evidence of carcinoid syndrome, including serotonin-related flushing, edema, and less frequently diarrhea [5, 86, 93]. The diagnosis of primary renal carcinoid tumor is incidental in 25–30 % of cases [86, 94]. Imaging studies show a heterogeneous tumor, with solid and cystic components. Calcification has been reported in ~1/4 of cases [86, 95]. The tumors show minimal enhancement by CT imaging [86, 96].

Pathology

On gross evaluation, renal carcinoid tumor is well circumscribed and soft and shows a homogenous white-yellow cut surface. Calcifications, hemorrhage, and cystic change may be present [5, 86]. On microscopic review, tumor cells can show ribbonlike, trabecular, rosette-like, and rarely nested patterns (Fig. 9.8a) [5, 86]. Tumor cells have a monotonous appearance. Nuclei are relatively uniform and round and contain finely

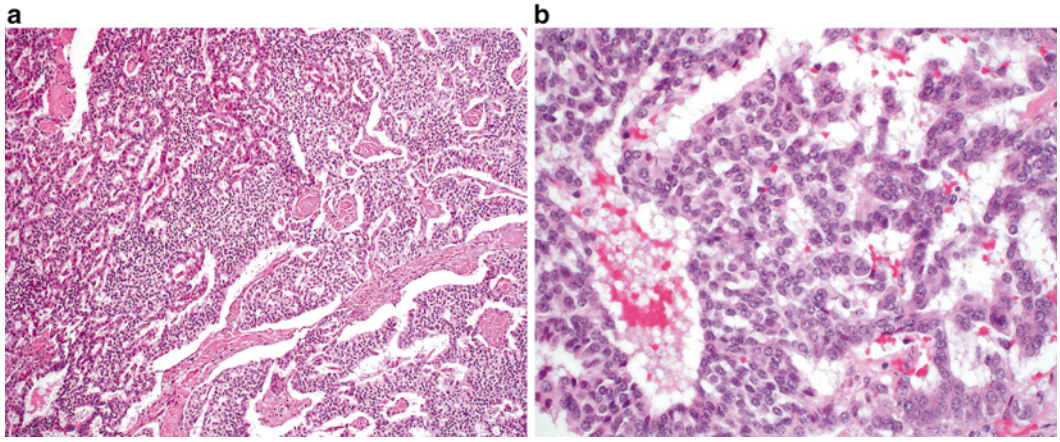

Fig. 9.8 Renal carcinoid tumor. (**a**) This example shows both trabecular and nested growth patterns. (**b**) Nuclei show the characteristic granular chromatin pattern associated with carcinoid lesions

granular chromatin (Fig. 9.8b) [5, 86, 89]. Rarely, moderate nuclear atypia or mitotic figures can be identified.

The genetic profile of renal carcinoid tumor has not been defined due to a small number of cases studied. One study has reported heterozygosity of 3p21 [5, 97].

The immunohistochemical profile of renal carcinoid is similar to neuroendocrine tumors in other locations. Synaptophysin and chromogranin are positive in the majority of tumors [5, 89, 98]. In addition, tumor cells can show dot-like immunoreactivity for CAM5.2 and may be positive for vimentin and cytokeratin 7 [89]. Renal carcinoid tumor is negative for TTF-1, WT-1, PAX2, and PAX8 [5, 89, 98].

Renal carcinoid tumor should be differentiated from other lesions that demonstrate neuroendocrine features, including small cell carcinoma, primitive neuroectodermal tumor (PNET), pheochromocytoma, and neuroblastoma. Small cell carcinoma is distinguished by the presence of classic features that include frequent mitotic features, apoptotic debris, necrosis, and nuclear molding. Morphology and clinical information is most helpful, as CD99, and typical neuroendocrine markers will not distinguish these entities [89, 98]. S100 immunostain may be helpful when neuroblastoma and pheochromocytoma (sustentacular cells) are in the differential diagnosis. Metastases from other primary sites (such as the gastrointestinal tract) should be clinically excluded. Of note, PAX8 expression supports the diagnosis of a metastatic carcinoid as primary renal carcinoids have been shown to be negative for PAX8, whereas a subset of GI primary carcinoid tumors are positive for polyclonal PAX8 [98–100].

Prognosis and Clinical Management

Distant metastases to the liver, bone, and orbit have been reported [82, 85, 86, 89].

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