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Rare (<1%) histological subtypes of renal cell carcinoma: an update

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Abstract

Recent advances in genetics and pathology have allowed description of several new histological subtypes of renal cell carcinoma (RCC) as well as better characterization of other rare subtypes. We herein present a comprehensive review of taxonomy, epidemiology, pathology, imaging findings, and natural history of a wide spectrum of rare subtypes of RCCs that individually constitute <1% of all the RCCs.

Key words: Renal cell carcinoma—Collecting duct carcinoma—Renal medullary carcinoma—Oncocytoid carcinoma

Renal cell carcinoma (RCC) is the most common primary renal epithelial malignancy. RCC constitutes 8th most common malignancy in adults, accounting for 3%–4% of new cancer cases and 3% of all cancer deaths in the United States [1]. It is now well established that RCC consists of several distinct histological subtypes with characteristic tumor histology and biology. According to Mainz classification schemata proposed in 1986, RCCs were categorized into clear cell, papillary, and chromophobe subtypes. Significant advances in understanding of the genetic basis of diverse pathologic subtypes of RCCs over the last two decades led to the adoption of WHO classification system in 2004 based on morphological, immunohistochemical, and molecular findings [2]. Clear cell carcinoma is the most common subtype of RCCs (70%), followed by papillary (15%) and chromophobe (5%) subtypes. In addition, several new histological variants, some with distinct epidemiology, pathological findings, clinico-biological behavior, and imaging manifestations were described. These uncommon sporadic and rare familial RCCs constitute the remaining 10% of RCCs. Select RCCs in children and young adults include renal medullary carcinoma (RMC) seen exclusively in patients with sickle cell trait/disease, oncocytoid carcinomas in neuroblastoma survivors, and translocation carcinomas that show marked proclivity to lymph node metastases. Collecting duct carcinoma (CDC), a biologically aggressive RCC, predominantly affects elderly males and presents at an advanced stage with poor prognosis. Mucinous, tubular, and spindle cell cancers (MTSCCs) are low grade, distal nephron tumors which predominantly affect women. Distinctive epidemiology, histo-morphology, cytogenetics, clinical manifestations, and imaging features of these rare sporadic subtypes of RCC are presented.

Collecting duct carcinoma (CDC)

CDC, as the name suggests, is thought to originate from or recapitulate the epithelia of distal collecting tubules. CDC predominantly affects men in their 4th–7th decade

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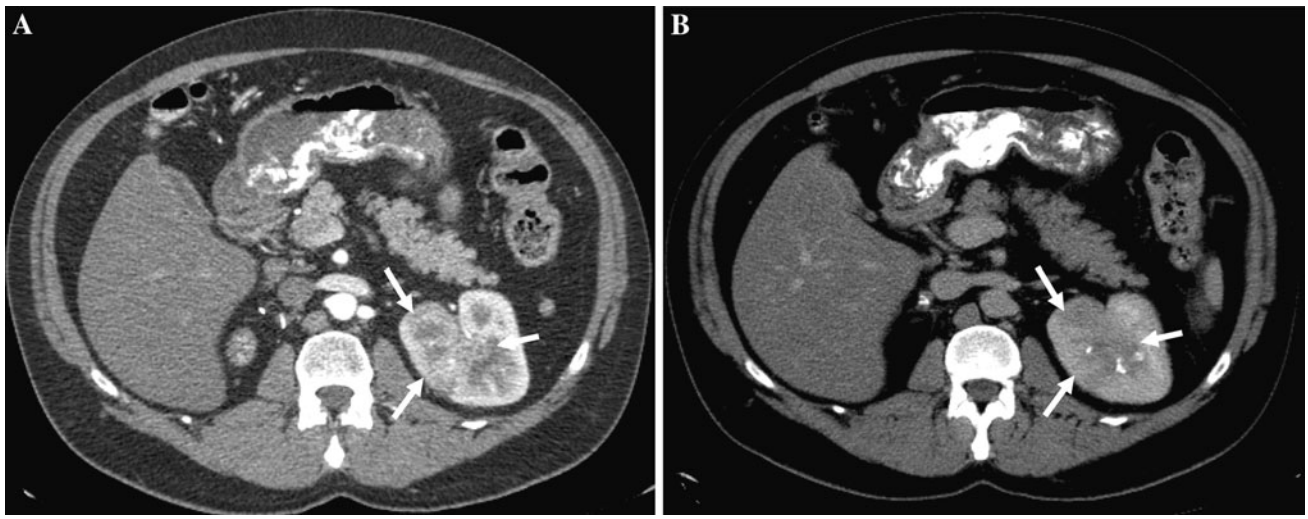

Fig. 1. Axial contrast-enhanced CT scan images in the corticomedullary (**A**) and nephrographic (**B**) phase in a 48-year-old male demonstrate a diffusely infiltrating hypovascular mass in the upper pole of left kidney (*arrows*) that proved to be a collecting duct carcinoma on surgical excision and histopathological analysis.

of life (mean age: 55 years; M: F—2:1) and is an aggressive cancer which often presents at an advanced stage [3–5]. CDCs represent 0.4%–1.8% of all RCCs in the western population [6]. Due to rapid growth and early metastases, CDCs are symptomatic early in the disease course. Clinical presentation is similar to that of classical RCC and includes hematuria, flank pain, abdominal mass, anorexia, and weight loss.

Pathologically, small CDCs are usually confined to medulla and appear white to gray on cut surface with firm consistency and frequent areas of necrosis. On histology, CDCs demonstrate infiltrative tubular or tubulopapillary pattern of growth with a characteristic desmoplastic stromal reaction and a chronic active inflammatory infiltrate. CDCs exhibit immunoreactivity to markers of distal collecting tubule, namely, lectins, cytokeratins in addition to vimentin, confirming their site of origin [7]. There is limited data on cytogenetic alterations in collecting duct carcinoma. Specific genetic alterations involving chromosomes 1, 6, 14, 15, and 22 have been reported in some cases [3].

On imaging, small CDCs are typically located within the renal medulla [8]. Most tumors are, however, large at the time of diagnosis and tend to exhibit an infiltrative growth pattern and involve the cortex and the medulla (Fig. 1) [9]. On ultrasound, these may be hyper-, iso-, or hypo-echoic to the renal parenchyma (Fig. 2). On CT and MR imaging, CDCs appear as large heterogeneous masses with areas of necrosis/cystic change, hemorrhage, and dystrophic calcifications. They typically show weak and heterogeneous enhancement on post contrast studies [10]. Involvement of the renal sinus and renal pelvis is commonly seen, hence simulating urothelial malignancy [11, 12]. Presence of a large cystic component with retroperitoneal lymphadenopathy has been reported to occur more commonly with CDC than conventional RCC (Fig. 3) [12]. Low signal intensity on T2-weighted images has also been reported, similar to papillary RCC.

CDCs are aggressive tumors with up to 40% patients presenting with metastases at the time of diagnosis. CDCs commonly metastasize to lymph nodes, adrenal glands, bone, lungs, and liver. Lymphadenopathy is seen in 44%–56% cases and distant metastases in one-third of patients with CDC [2, 10, 13]. Surgical resection is not curative in majority of patients, and mortality has been reported in up to two-thirds of patients within 2 years of surgery [14]. Immunotherapy and/or chemotherapy also has limited role in their management.

Renal medullary carcinoma (RMC)

RMC is a distinct subtype of RCC which occurs almost exclusively in children and young adults with sickle cell trait and sickle cell disease. RMC was first designated as a distinct pathologic entity in 1995 [15] and less than 130 cases of RMC have been reported so far in world literature [16]. Although the vast majority of patients in RMC are young African-American males (<10 years; M:F—5:1), this tumor has been reported in a wide age range (5–69 years) with isolated case reports in individuals without sickle cell trait or disease [17].

Gross hematuria (60%), flank pain (50%), and weight loss (25%) are the most common presenting symptoms of RMC [15]. Other manifestations include palpable flank mass and enlarged lymph nodes. Given the classical association of sickle cell trait with RMC, any of the

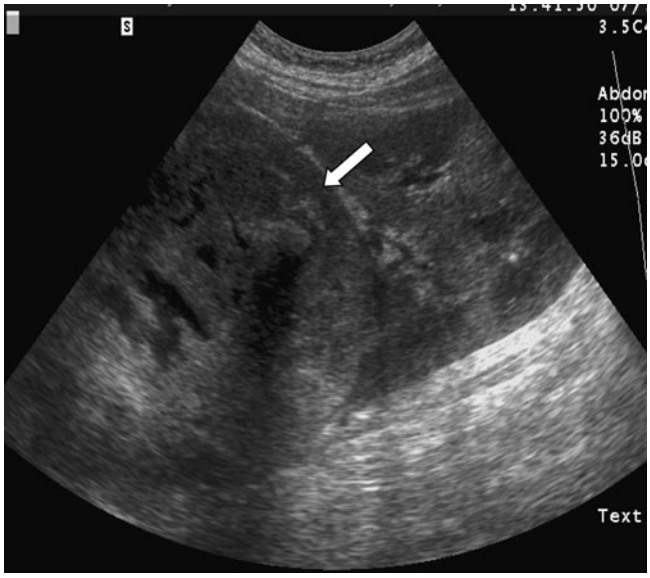

Fig. 2. Gray-scale ultrasound image of the right kidney in a 70-year-old male demonstrates a large heterogeneous mass arising from the right kidney. Surgical pathology confirmed the diagnosis of collecting duct carcinoma.

above symptoms in a patient with sickle cell trait should raise the suspicion for RMC. RMC is known as the "seventh sickle nephropathy" [15].

More than three-fourths of RMCs occur in the right kidney and appear as solitary, poorly circumscribed masses on gross pathology with frequent areas of necrosis and hemorrhage. Histologically, RMC is characterized by the presence of poorly differentiated eosinophilic cells in a characteristic fibro-inflammatory stroma [8]. Sickled erythrocytes are seen in and around the tumor. Cytogenetic anomalies which have been reported in RMC include monosomy of chromosome 11, translocations involving chromosome 3 and 8 and tetraploidy with bcr/abl translocations involving chromosomes 9 and 22. Genetic locus in chromosome 11 encoding the beta-globin gene has been proposed to play a central role in the pathogenesis of RMC [18].

On imaging, renal medullary carcinoma manifests as an infiltrative mass situated deep within the parenchyma and when small, and can be localized to the medulla. These tumors show heterogeneous contrast enhancement due to hemorrhage and necrosis (Fig. 4). Caliectasis and regional lymphadenopathy are also common [19]. Infiltrative renal masses in patients with sickle cell traits should be considered as RMC unless proven otherwise.

RMCs tend to be biologically aggressive with very poor prognosis, and metastases are seen in up to 95% of patients at presentation or shortly thereafter [17]. Common sites of metastases in descending order of frequency include lymph nodes (69%), lung (44%), liver (16%), and adrenal glands (15%) [17]. Advanced stage at diagnosis and relative resistance to chemotherapy decrease the median survival time of patients with RMC to be as low as 3 months. Early diagnosis and treatment may dramatically change the survival time, with reports of survival for up to 8 years in well-circumscribed, non-metastatic tumor [20, 21]. The current treatment options include surgical resection and chemotherapy with a variety of agents, which includes but not limited to MVAC (Methotrexate, Vinblastine, Doxorubicin, and Cisplatin), Interleukin, and Interferon therapy [17, 21]. Chemotherapy has been shown to prolong the survival in some patients [22]. None of the currently available treatment options are effective in treating advanced renal medullary carcinomas [17].

Mucinous tubular and spindle cell carcinoma

Mucinous tubular and spindle cell carcinoma were described as a distinct subtype of RCC in the 2004 WHO classification [23]. As indicated by its name, MTSCC is a tumor with predominant tubular and spindle cell morphology with excessive mucin production. MTSCCs can occur in a wide age range of patients (17–82 years; mean: 53 years) and demonstrates a striking female preponderance (F:M = 4:1) [9]. Clinically, MTSCCs can be asymptomatic or present with non-specific symptoms. MTSCCs have been frequently associated with nephrolithiasis; the cause and effect relationship between these two entities is, however, poorly understood [24].

MTSCCs are believed to originate from or resemble the distal nephron epithelium [25]. On gross examination, MTSCCs are well-circumscribed, non-infiltrating tumors with elastic consistency, and appear gray or light tan with rare necrosis and hemorrhage [24]. Histological hallmark of MTSC is the presence of cuboidal and spindle cells with low-grade atypia, in a mucinous extracellular matrix [23] (Fig. 5). On immunohistochemistry, MTSCCs demonstrate positive staining for cytokeratin, EMA, AE1/AE3(+), CK7(+), CK19(+), E-cadherin(+), and AMACR(+) suggesting a distal tubular origin [26] [23]. Cytogenetically, MTSCCs have been associated with genetic loss involving multiple chromosomes [26].

On imaging, MTSCCs have variable manifestations and appear as well-circumscribed, hypovascular masses that seem to arise from the cortex (Fig. 6). Occasional calcification may be seen. Larger tumors (>4 cm) show areas of hemorrhage and necrosis. Signal intensity on T2-weighted MR image may vary from low to intermediate thereby potentially mimicking papillary RCC [27].

MTSCCs are low grade, indolent malignancies, usually cured by surgery with very low rates of recurrence or metastases [28]. Local recurrence, regional lymphadenopathy, and distant metastases have been rarely described to occur in MTSCCs with high nuclear grade or sarcomatous transformation [26, 29–32].

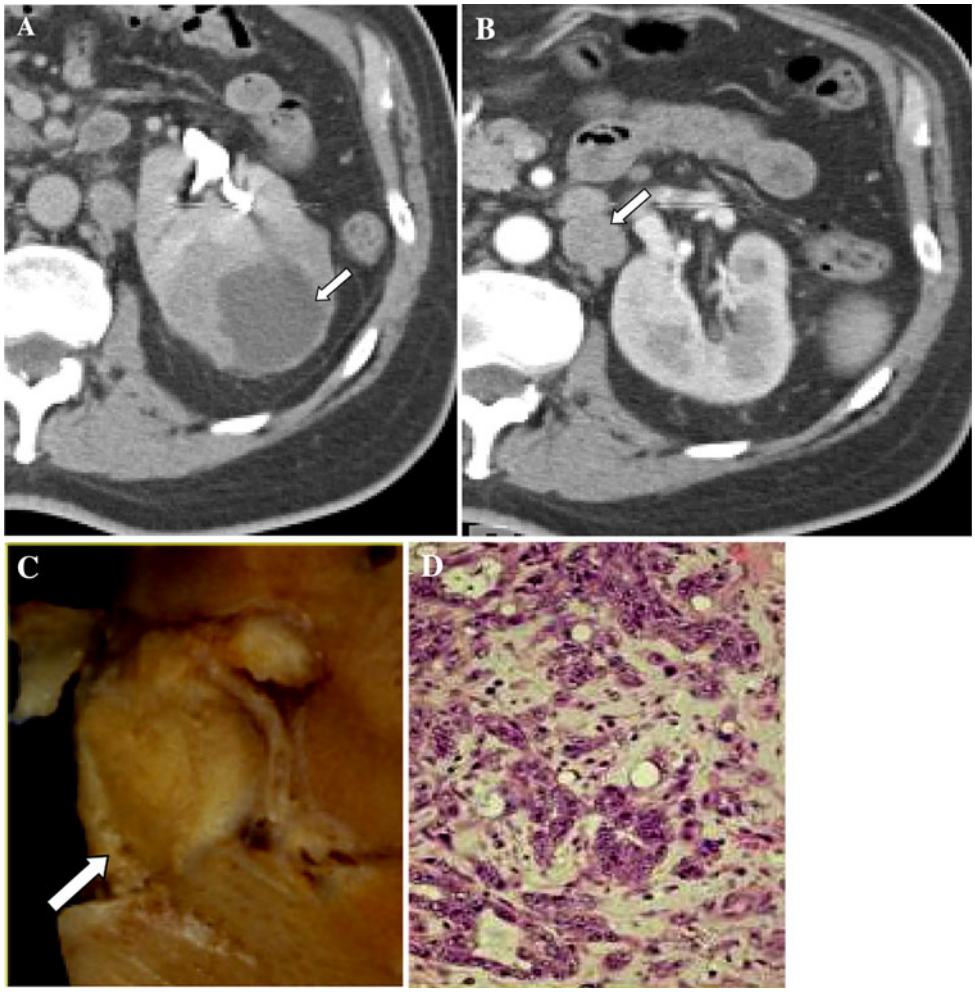

Fig. 3. Axial contrast-enhanced CT scan image demonstrates a heterogeneously hypodense mass in the left kidney (*arrow* in **A**) with para-aortic lymphadenopathy (*arrow* in **B**). Surgical resection and histopathological analysis confirmed the diagnosis of collecting duct carcinoma. Gross pathology of CDC in a different patient (**C**) demonstrates the mass to be relatively homogeneous with yellowish tinge on cut surface. Photomicrograph (**D**) demonstrates infiltrative tubular pattern with fibro-inflammatory stroma.

Tubulocystic RCC

Tubulocystic RCC is a distinctive rare subtype of RCC with unique pathological features. Tubulocystic RCC is, however, not considered as a distinct subtype in the 2004 WHO classification. Tubulocystic RCC is composed of tubules and duct-like structures and hence is presumed to originate from collecting duct. Tubulocystic RCC predominantly affects men in their 5th or 6th decade (M:F = 7:1), often asymptomatic or with non-specific symptoms [33, 34]. On gross pathology, tubulocystic carcinoma appears as well-circumscribed cystic lesions with rare areas of hemorrhage and necrosis. Microscopically, the tumor consists of variable-sized tubules and cysts lined with cells containing abundant eosinophilic cytoplasm, with intervening septa. Typically, solid growth pattern is lacking, accounting for purely cystic appearance on gross pathology and on imaging. Tubulocystic RCC may coexist with papillary RCC and in fact is thought to be a variant of papillary RCC by some authors [34].

On imaging, tubulocystic RCC appears as cystic mass with varying degrees of complexity. Some tumors appear as multiloculated cysts with thin enhancing septa and varying degrees of hemorrhage in the locules. More commonly, the cysts are very small giving them a spongy pattern of appearance on contrast-enhanced CT (Fig. 7). Hence these lesions tend to be classified as Bosniak Type III or type IV lesions. Differential diagnosis of tubulocystic RCC on imaging includes cystic nephroma, multilocular cystic RCC, and mixed epithelial and stromal tumor of kidney. Tubulocystic RCCs are generally considered a tumor with low malignant potential. Nevertheless, there is limited data on biological behavior of these tumors and recurrence and metastases have been reported [34, 35].

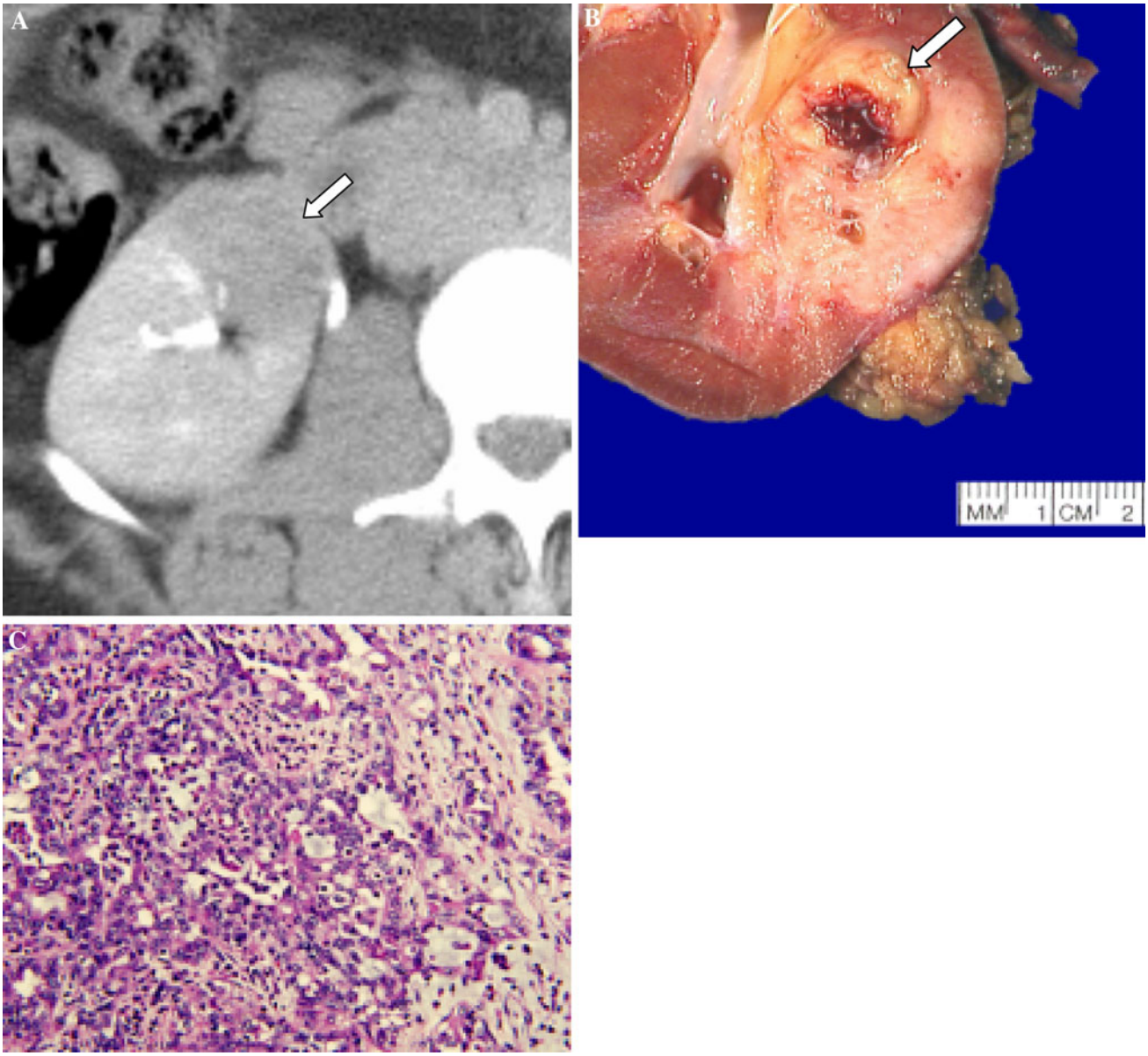

Fig. 4. Renal Medullary Carcinoma in a 35-year-old male with sickle cell trait. Axial contrast-enhanced CT (**A**) demonstrates an ill-defined hypodense lesion along the anterior interpolar cortex of the right kidney (*arrow*). Cut surface from gross-specimen (**B**) reveals a heterogeneous mass with area of necrosis and hemorrhage. Surgical pathology confirmed the diagnosis of renal medullary carcinoma with sheets of poorly differentiated cells with infiltrative growth pattern interspersed with inflammatory infiltrates on histology (**C**).

Xp11 translocation RCC

Translocation RCC is a tumor of children and young adults with an average age of presentation of 25 years. Around 160 cases have been reported so far, and this tumor tends to exhibit a female preponderance (M:F—1:2.5) [36, 37]. African-Americans have an increased tendency to develop this type of RCC [38]. Incidence of this tumor in adults and young patients is less than 1%; more recently, there has been an increasing incidence of this tumor in adults above 40 years [37, 39]. Clinically, Xp11 translocation RCCs present with symptoms similar to other subtypes of RCC, such as flank pain, hematuria, weight loss, or anemia; a substantial number of tumors may incidentally be found during imaging.

Translocation RCCs typically arise from the renal cortex. Grossly, translocation RCC resembles clear cell RCC and appears as well-circumscribed, cortical, or subcapsular lesion with variegated tan yellow appearance on cut surface [36]. Foci of necrosis and hemorrhage may also be seen [37, 40]. Histologically, translocation RCCs

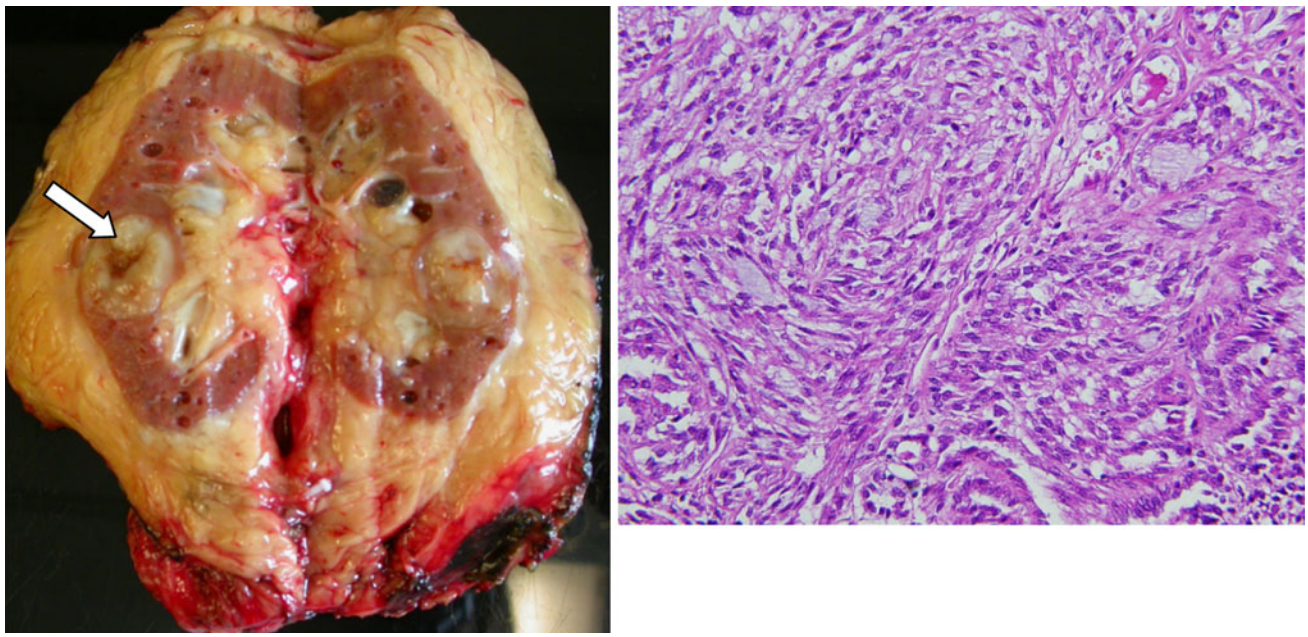

Fig. 5. Gross- and microscopic features of mucinous tubular and spindle cell carcinoma (MTSCC). The tumor appears heterogeneous with yellow-tan cut surface and areas of hemorrhage (*arrow*). Histological features of a prominent spindle cell pattern interspersed with stromal mucin are characteristic.

demonstrate heterogeneous architecture with cells arranged in broad sheets, nests, trabeculae, true papillary, or pseudopapillary pattern. Bulging cell borders result in a typical soap bubble pattern [41]. These tumors mimic other RCC subtypes such as clear cell carcinoma and papillary carcinoma because of their architectural heterogeneity [39].

More than 90% of translocation in this subtype of RCC involves transcription factor E3 (TFE3) gene located on Chromosome Xp11. Immunohistochemistry thus helps in differentiating translocation carcinomas from other histological subtypes, as it detects aberrant nuclear overexpression of the TFE3 gene product (typical of translocation carcinoma). Sensitivity of immunohistochemistry has been shown to be up to 97.5% and specificity to be up to 99.6% in detecting translocation RCCs [36, 42].

On imaging, small translocation carcinomas are localized to the cortex, are well demarcated, and show weak post contrast enhancement. On MRI, they are known to show low signal on T2-weighted images thereby overlapping with the appearances of papillary RCC [43]. Larger tumors, however, are heterogeneous with frequent areas of hemorrhage and necrosis (Fig. 8). These tumors commonly tend to be expansile. Dense tumor calcifications occasionally are seen which can cause obstruction of the renal pelvis, thereby promoting extensive xanthogranulomatous pyelonephritis thereby obscuring the tumor [39]. Nearly two-thirds of translocation RCCs present at a more advanced stage compared to other RCCs [40]. Common sites of metastases include lung, liver, and brain [44]. Lymphadenopathy is also common and has been reported to occur in 24%–85% of patients. Tumors with certain translocation types t(X;17) (p11.2;q25) are more likely to present with lymphadenopathy compared to others. These tumors, however, may show a benign course in spite of advanced stage at presentation [36, 40, 44]. Distant metastasis is, however, considered a grave prognostic factor with poor survival [44].

RCCs associated with end-stage renal disease

Acquired cystic kidney disease (ACKD), by definition, is the presence of multiple renal cysts which occupies at least 25% of renal mass. ACKD affects 8%–13% of end-stage kidneys before dialysis and up to 50% of patients undergoing dialysis. The duration of dialysis also affects the development of ACKD, and up to 87% of patients undergoing dialysis develop ACKD after 9 years. The association between RCC and ACKD was first described by Dunhill et al. [45]. Prevalence of RCC in end-stage renal disease patients is four times that of general population (1.64% vs. 0.04% in general population). Overall, an estimated 46% of end-stage kidneys have acquired cystic disease-associated RCC with up to 70% of harboring more than one tumor in a single kidney. Men are affected more frequently than women and these are generally less aggressive than sporadic RCC.

The pathogenesis of RCC in ACKD is unknown, but likely involves deposition of oxalate crystals, decreased

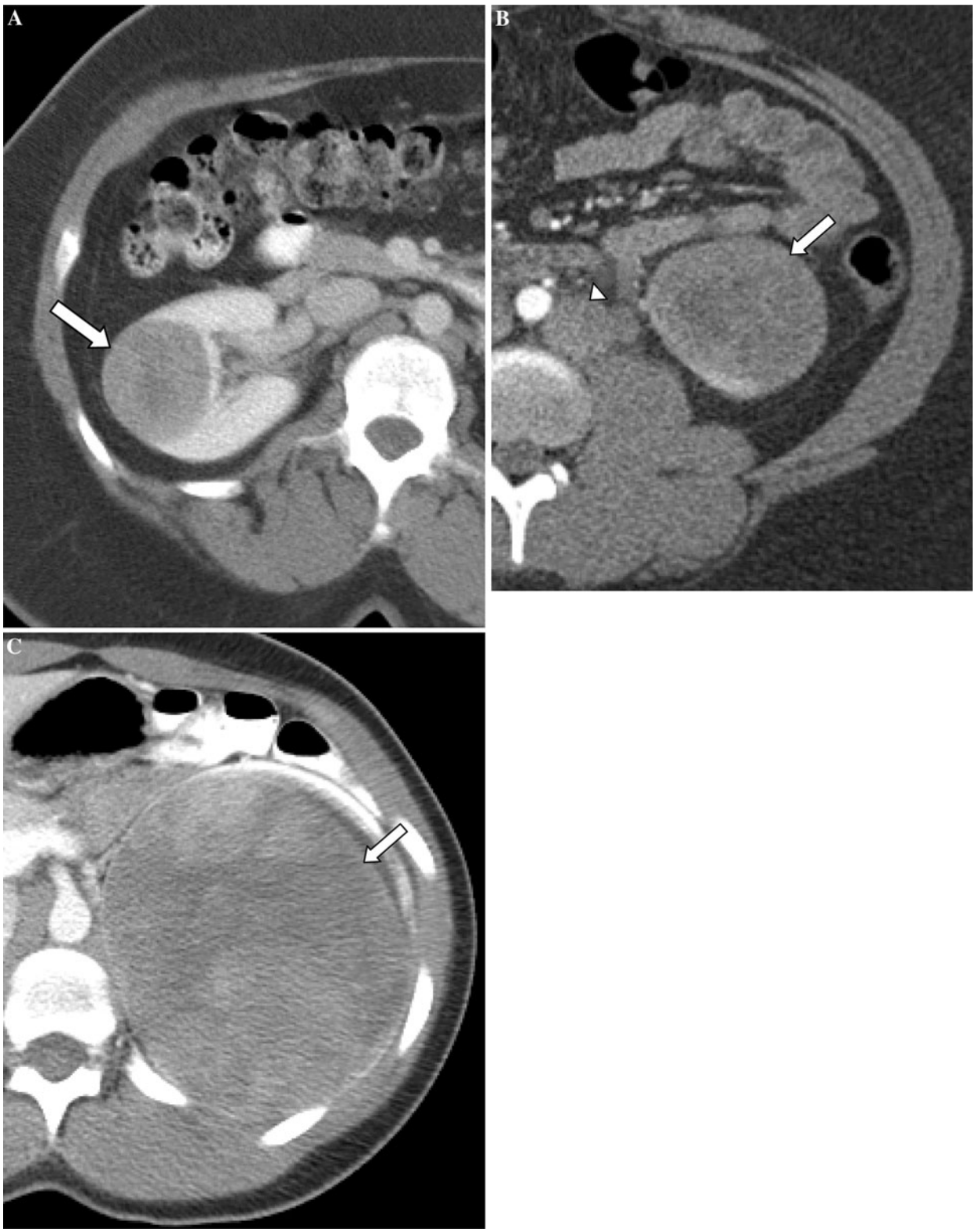

Fig. 6. Imaging spectrum of histologically confirmed mucinous tubular and spindle cell carcinomas (MTSCCs). Axial contrast-enhanced CT scan image (**A**) demonstrates a well-defined hypodense lesion in the right kidney (*arrow*). Axial contrast-enhanced CT scan image (**B**) demonstrates a large relatively homogeneous low density lesion in the lower pole of the left kidney (*arrow*) with metastatic retroperitoneal lymphadenopathy (*arrowhead*). Axial contrast-enhanced CT scan image (**C**) demonstrates a large well-defined mass arising from the left kidney (*arrow*).

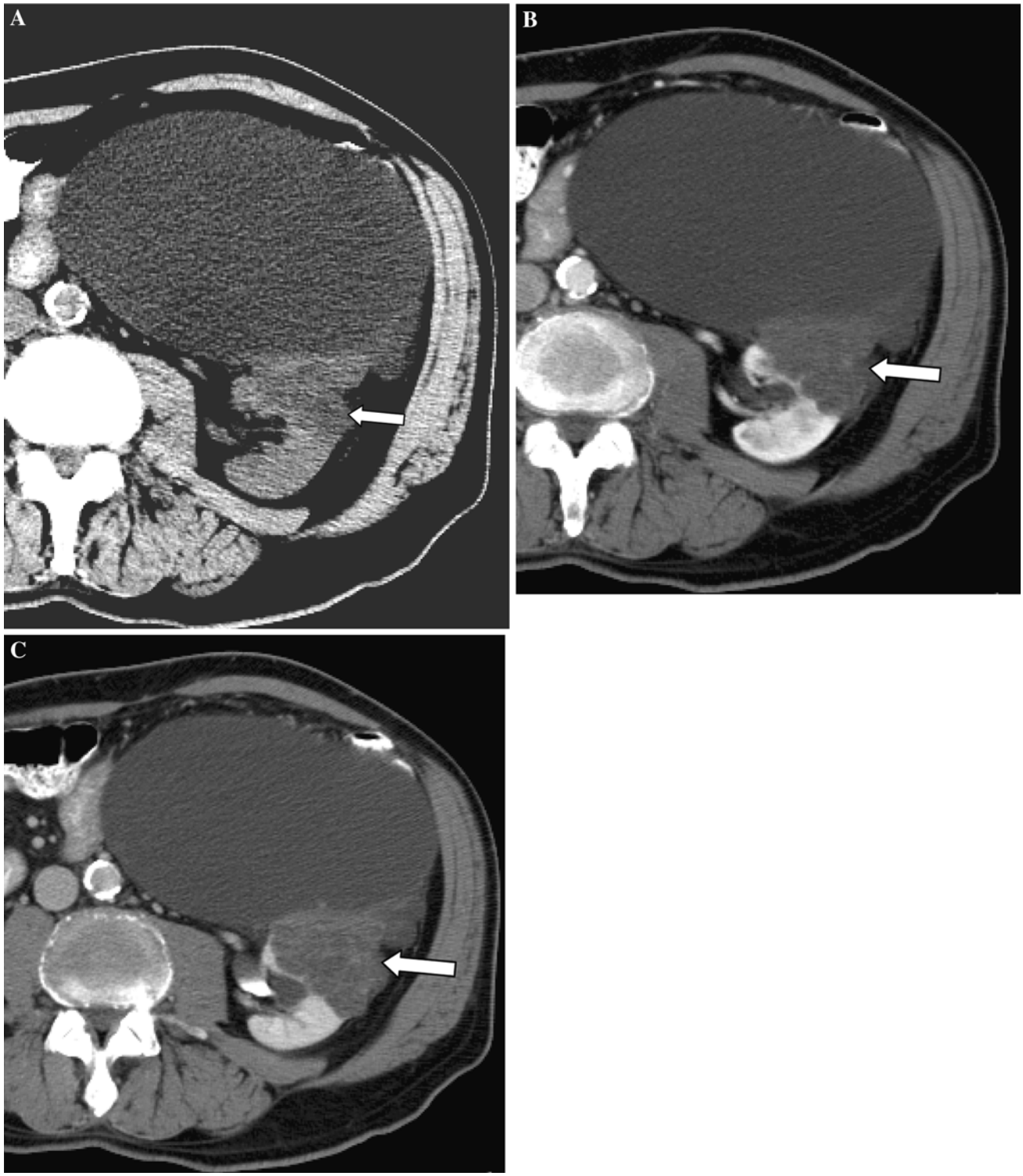

Fig. 7. Tubulocystic renal cell carcinoma. Axial unenhanced (**A**), contrast-enhanced CT scan images in the nephrographic (**B**), and excretory (**C**) phases demonstrate a multiloculated cystic lesion with enhancing septations in the upper pole of the left kidney (*arrows*). Surgical excision and histopathological analysis confirmed the diagnosis of tubulocystic renal cell carcinoma.

immunity, increased free radical production related to inflammation, and impaired anti-oxidant defense mechanisms. Renal transplantation has been shown to decrease the incidence of ACKD [46]. Two distinctive subtypes of RCC have been described in ACKD. These include acquired cystic disease-associated RCC (present in nearly one-half of all ACKD, two-thirds arise within a cyst) and papillary clear cell RCC (prominent cystic

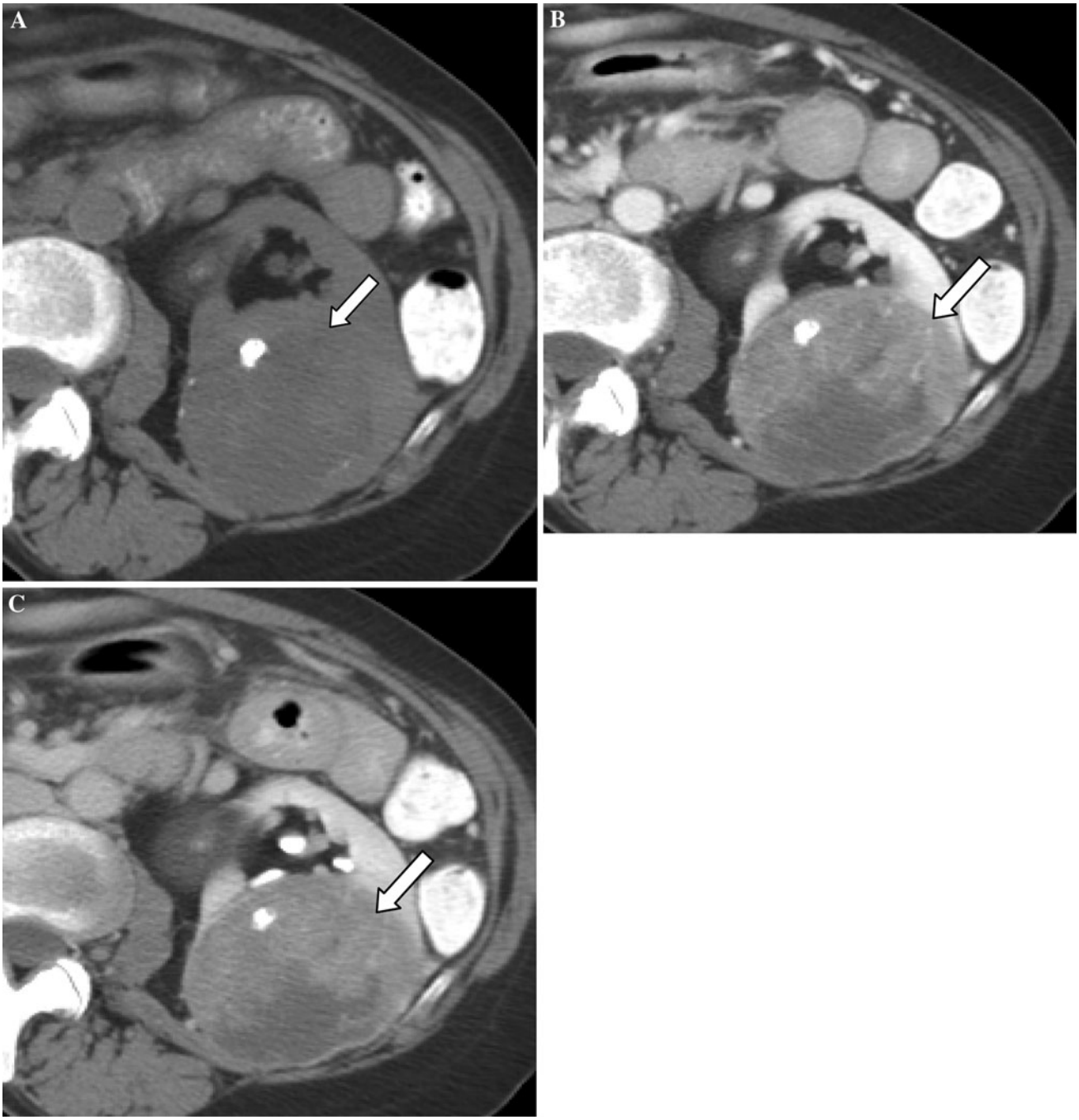

Fig. 8. Xp11 translocation carcinoma in a 43-year-old man. Axial unenhanced (**A**), contrast-enhanced images in the nephrographic (**B**), and excretory phase (**C**) demonstrates a large well-defined mass lesion in the left kidney (*arrows*) which shows areas of necrosis and calcification. Surgical resection and histopathological analysis confirmed the diagnosis of Xp11 translocation renal cell carcinoma.

component in up to 50%) [47] (Fig. 9). The predominant histological subtype in patients on dialysis of less than 10 years duration is conventional clear cell RCC, with the ACKD-associated RCC predominating those on dialysis of more than 10 years duration [48].

On imaging, presence of small kidneys with multiple cysts of varying size and attenuation should promptly alert the reader to evaluate for presence of RCC (Fig. 10). Often the tumor is subtle, and differentiating an RCC from innumerable cysts of varying complexity (hemorrhagic, proteinaceous, or benign septated cysts) is challenging. MRI would be beneficial in this setting. Presence of solid enhancing mass or complex cystic lesion with enhancing septations and solid components in an individual with atrophic kidneys and multiple cysts should raise suspicion for RCC in ACKD.

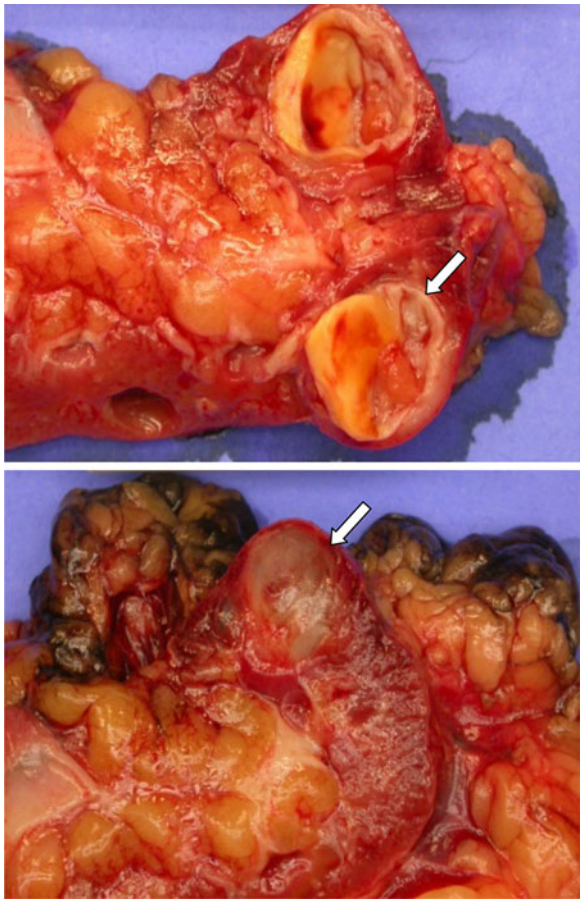

Fig. 9. Gross specimens demonstrating ACKD-associated renal cell cancer with the presence of multiple cysts and a solid renal mass in both the kidneys (*white arrows*).

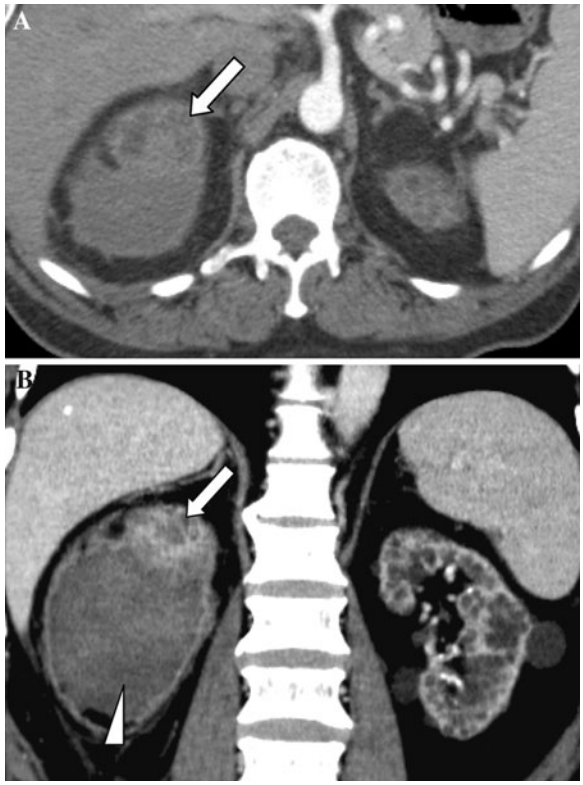

Fig. 10. ACKD-associated renal cell carcinoma. Axial (**A**) and Coronal (**B**) contrast-enhanced CT scan images in the arterial and venous phases, respectively, demonstrate a heterogeneously enhancing mass in the upper pole of the right kidney (*arrows*) with persistent enhancement in the venous phase. Also, seen is a large perinephric hematoma (*arrowhead*).

Routine screening for RCC in dialysis patients is, however, controversial and screening recommendations are not yet standardized. Schwarz et al. following his study of 561 transplant patients recommended that annual ultrasound screening of their native kidneys should be performed on all transplant patients. Based on Bosniak category, additional recommendations for those with ACKD were proposed [49]. For example, patients with Bosniak Type 1 or type 2 cysts should be scanned every 6 months and patients with Bosniak type 2F cysts should be followed every 3 months. However, ACKD need not always precede renal neoplasia in dialysis patients, and ultrasound has limited accuracy in differentiating cystic neoplasms from other benign complex cysts [50]. There is very limited data on prognosis of ACKD-associated renal cell cancer.

Oncocytoid RCC

Oncocytoid RCC is a subtype of RCC that occurs exclusively in neuroblastoma survivors. It is estimated that neuroblastoma survivors have more than 300-fold increased risk of developing RCC, most presenting 3–11 years after the initial diagnosis of neuroblastoma [51] [52, 53]. Genetic susceptibility, familial cancer syndromes, and exposure to chemo-radiation have all been implicated in this increased risk of secondary malignancy. Oncocytoid RCCs tend to occur in a wide age range (2–35 years; median age—14.5 years), and do not exhibit sex predilection. Clinically, Oncocytoid RCCs can be asymptomatic or present with non-specific symptoms of abdominal pain, abdominal mass, or fatigue.

Oncocytoid RCCs vary in size from 3.5 to 8 cm in diameter, and can be confined to kidney or present with renal vein invasion, extracapsular extension and regional or distant metastases [52, 53]. Microscopically, these tumors have oncocytoid cells with abundant eosinophilic material arranged in sheets or nests and has papillary or solid growth pattern [52].

Imaging findings are non-specific and may not be distinguished from clear cell RCC. The tumor can vary in size and enhancement pattern depending on the degree of cellularity, vascularity, and necrosis (Fig. 11).

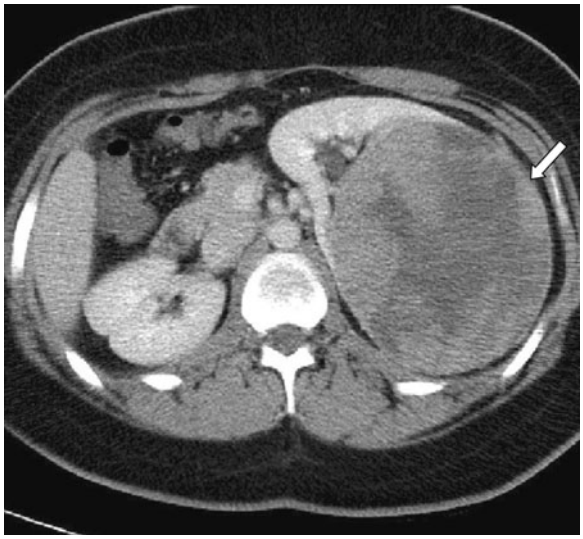

Fig. 11. Oncocytoid renal cell carcinoma in a patient with history of neuroblastoma. Axial contrast-enhanced CT scan image through the kidneys reveal a large exophytic heterogeneous mass in the left kidney.

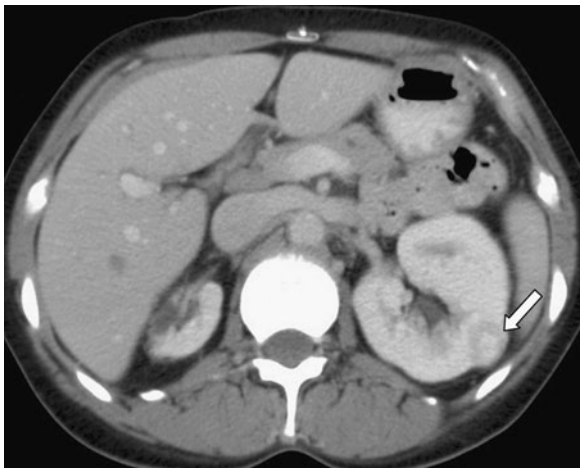

Fig. 12. Leiomyomatous renal cell carcinoma. Axial contrast-enhanced CT scan image reveals a small heterogeneously enhancing lesion in the left kidney which was proven to be a leiomyomatous RCC on surgical pathology.

An imaging diagnosis can, however, be suggested if a history of treatment for neuroblastoma is available.

Leiomyomatous RCC

RCC with angioleiomyoma-like stroma or leiomyomatous RCC is a recently described subtype with only a handful of cases reported so far in the literature. This tumor can affect a wide age group of population (2nd through 9th decade) with varying tumor size (1.8–14 cm) [2]. Histologically, leiomyomatous RCCs are composed of epithelial cells in solid, tubular, or papillary architecture interspersed with smooth muscle stroma and occasional dilated vascular spaces [2]. The clinical and imaging manifestations are not specific and indistinguishable from conventional RCC (Fig. 12). The data is too sparse to establish natural history and prognosis.

Conclusion

A wide spectrum of rare histological subtypes of RCC exists, some with characteristic epidemiology and clinicobiological behavior. Imaging features in conjunction with corroborative history such as age, history of sickle cell disease, and neuroblastoma assist in making the correct diagnosis. Knowledge of evolving histogenesis, tumor biology, disease distribution, and natural history of these tumors help understand the diversity of renal malignancies with attendant therapeutic and prognostic implications.

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