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Clinicopathological characterisation of renal cell carcinoma in young adults: a contemporary update and review of literature

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Clinicopathological characterisation of renal cell carcinoma in young adults: a contemporary update and review of literature

Aims: Renal cell carcinomas are relatively rare in children and young adults. While well characterised in adults, the morphological and molecular characterisation of these tumours in young patients is relatively lacking. The objective of this study was to explore the spectrum of renal cell carcinoma (RCC) subtypes in children and young adults and to determine their clinico–pathological, immunohistochemical and molecular characteristics by evaluating a large retrospective cohort of renal cell carcinoma patients age 30 years or younger.

Methods and results: Sixty-eight cases with confirmed diagnosis of renal cell carcinoma at age 30 years or younger were identified at our institution. Clear cell carcinoma accounted for the most common subtype seen in this age group. Translocation renal cell carcinoma and rare familial syndrome subtypes such as succinate dehydrogenase deficient renal cell carcinoma and tuberous sclerosis complex-associated renal cell carcinoma were found relatively more frequently in this cohort. Despite applying the 2016 WHO classification criteria, a high proportion of the tumours in our series remained unclassified.

Conclusions: Our results suggest that renal cell carcinoma in children and young adults is a relatively rare disease that shares many histological similarities to renal cell carcinoma occurring in adults and yet demonstrate some unique clinical–pathological differences. Microphthalmia-associated transcription (MiT) family translocation RCC and rare familial syndrome subtypes are relatively more frequent in the paediatric and adolescent age groups than in adults. Clear cell RCC still accounted for the most common subtype seen in this age group. MiT family translocation RCC patients presented with advanced stage disease and had poor clinical outcomes. The large and heterogeneous subgroup of unclassified renal cell carcinoma contains phenotypically distinct tumours with further potential for future subcategories in the renal cell carcinoma classification.

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Introduction

Renal tumours comprise a diverse spectrum of neoplastic lesions with patterns that are relatively distinct for children and young adults. Adult renal cell carcinomas (RCCs) comprise 6% of all cancers, with a peak incidence in the sixth decade. Clear cell renal cell carcinoma (CCRCC) is the predominant subtype in older patients.[1] In children and young adults, renal cell carcinomas are rare, accounting for 2% of paediatric renal tumours.[2] Paediatric renal cell carcinoma lacks the male:female gender predilection (2:1), as well as associations with environmental factors that are often present in adult renal tumours.[3–5] Additionally, prognosis and clinical outcomes have been reported to be significantly different between both age groups.[6]

In recent years, significant advances have been made in our knowledge of the genomic background of renal cell carcinomas. As a result, the 2004 World Health Organisation (WHO)[7] classification of renal tumours recognised new distinct entities, including Xp11.2 translocation renal cell carcinoma and syndrome-associated tumours. The morphological spectrum was further expanded in the 2016 WHO classification[8] to include entities such as hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma (HLRCC-associated RCC), succinate dehydrogenase-deficient renal cell carcinoma (SDH)-deficient RCC, tubulocystic renal cell carcinoma, acquired cystic disease-associated renal cell carcinoma (ACD-RCC) and clear cell papillary renal cell carcinoma. While several studies have previously been published regarding the clinical features of renal cell carcinomas in young adults,[9–11] the morphological and molecular characterisations of these tumours, especially in recognition of the recent 2016 WHO classification, are lacking.

In this study, we sought to explore the spectrum of renal cell carcinoma subtypes in children and young adults and to determine their clinicopathological, immunohistochemical and molecular characteristics by evaluating a large retrospective cohort of renal cell carcinoma patients aged 30 years or younger.

Materials and methods

CASE SELECTION

After approval by the Institutional Review Board (IRB), a retrospective pathological and clinical review of renal cell carcinoma in patients aged 30 years or younger, diagnosed between January 1986 and December 2018 at the University of Michigan Health system, was conducted. Only patients who underwent definitive surgical treatment by partial or radical nephrectomy with histological material available for review were included. Electronic medical records and pathology reports were reviewed to analyse clinical parameters [age at diagnosis, sex, clinical stage, previous chemotherapy exposure, relevant family history, history of Von Hippel-Lindau (VHL) syndrome or other hereditary renal cell carcinoma syndromes, history of other tumours and end-stage renal disease (ESRD)], pathological variables (tumour size, focality and laterality) and follow-up data (vital status and presence of metastasis/recurrence).

Representative haematoxylin and eosin-stained whole tissue sections of each tumour were reviewed by three study pathologists (E.A., A.U. and R.M.) to evaluate the renal tumours as per the current (2016) WHO renal tumour classification criteria.[8] Tumours recognised as CCRCC, papillary renal cell carcinoma (PRCC), chromophobe RCC (ChRCC) and renal medullary carcinoma had the usual morphological features, as previously described.[7] Microphthalmia-associated transcription (MiT) family translocation renal cell carcinoma was considered by morphology if it displayed papillary or pseudopapillary architecture with distinctly voluminous cytoplasm in the majority of tumour cells; other morphological appearances as described previously were also taken into consideration.[12–14] SDH-deficient RCC was considered if tumours displayed the presence of cytoplasmic vacuoles and inclusion-like spaces containing eosinophilic fluid or flocculent material. Tuberous sclerosis complex-associated RCC (TSC-associated RCC) in patients with tuberous sclerosis was diagnosed if tumours displayed distinct morphological features, including features similar to tumours previously described as 'renal angiomyoadenomatous tumour', features similar to ChRCC or showed a granular-macrocystic morphology.[15]

Unclassified RCC was diagnosed when two different well-recognised histological features coexisted in different areas of the same gross tumour, or in cases where histological features and immunohistochemical profile were atypical or unusual, precluding classification into the RCC subtypes described above.

Tumour grade was assigned according to the WHO/ISUP grading system[16] and was applied to CCRCC and PRCC. All cases were staged according to the American Joint Committee TNM *Cancer staging manual*, 8th edition.

IMMUNOHISTOCHEMISTRY

The renal tumours were placed into their appropriate diagnostic categories using appropriate immunohistochemical stains as and when necessary. Representative paraffin-embedded tissue blocks were selected for immunohistochemistry, which was performed using commercially available antibodies at the University of Michigan according to standard protocols. When available, immunohistochemistry previously performed during the initial diagnosis of each case was reviewed.

A panel including pan-cytokeratin (CK) cocktail (AE1/3; Chemicon International, San Diego, CA, USA; 1:800), cytokeratin 7 (CK7; Dako, Carpenteria, CA, USA; 1:125, 30 min), cytokeratin 20 (CK20; Dako; 1:125, 30 min), carbonic anhydrase IX (CAIX; Novus Biologicals, Littleton, CO, USA; 1:200, 30 min), CD117 (Dako, 1:600), alpha-methylacyl-CoA racemase (AMACR; P504s; Zeta Corporation, Tuscon, AZ, USA; 1:20, 30 min), fumarate hydratase (FH), HMB45; Dako; 1:25, 30 min) and Melan-A (Dako; 1:50, 30 min) was employed as necessary.

CYTOGENETIC ANALYSIS

Fluorescence *in-situ* hybridisation (FISH) for *TFE3* and/or *TFEB* gene rearrangements were performed on representative formalin-fixed paraffin-embedded (FFPE) tumour tissue from cases that were morphologically suspicious for MiT family translocation renal cell carcinoma using our in-house dual-colour break-apart clinical *TFE3* and *TFEB* FISH assay using custom-made probes (Empire Genomics, Buffalo, NY, USA), according to the previously described procedure protocol.[12]

Results

A total of 68 cases with confirmed diagnosis of RCC at age 30 years or younger were identified and included in our study. The demographics and clinicopathological features of these patients and their tumours are detailed in Tables 1 and 2 and Table S1. The median age at diagnosis was 25.5 years (mean = 23, range = 7–30 years). The cohort consisted of 50% females (n = 34 of 68) and 50% males (n = 34 of 68). Sixty-three per cent of the patients (n = 43 of 68) underwent partial resection, whereas 37% (n = 25 of 68) had radical nephrectomy. The median tumour size at the time of surgical resection was 3.7 cm (mean = 5.3, range = 1.0–30.0 cm). The majority of the tumours presented as a single lesion (83%, n = 57 of 68), while 17% of the tumours (n = 11/68) were multifocal.

CCRCC was the most common histological subtype, with non-VHL- and VHL-associated RCCs making up 35% (n = 23 of 68) and 18% (n = 12 of 68) of the entire cohort, respectively. Other tumours identified in this cohort were MiT family translocation RCC (13%, n = nine of 68), RCC unclassified (12%, n = eight of 68), Type 1 PRCC (7%, n = five of 68), TSC-associated RCC (6%, n = four of 68), ChRCC (4%, n = three of 68), SDH-deficient RCC (3%, n = two of 68), Type 2 PRCC (1%, n = one of 68) and renal medullary carcinoma (1%, n = one of 68). Clear cell papillary RCC, HLRCC-associated RCC,

Table 1. Renal cell carcinoma histological subtypes in our patient cohort

	Number	Percentage
Tumour type		
CCRCC (non-VHL)	23	35%
CCRCC (VHL-associated)	12	18%
tRCC	9	13%
RCC, unclassfied	8	12%
Type 1 PRCC	5	7%
TSC-associated RCC	4	6%
ChRCC	3	4%
SDH-deficient RCC	2	3%
Type 2 PRCC	1	1%
Renal medullary carcinoma	1	1%

CCRCC, Clear cell renal cell carcinoma; tRCC, Translocation-associated renal cell carcinoma; PRCC, Papillary renal cell carcinoma; ChRCC, Chromophobe renal cell carcinoma; RCC, Renal cell carcinoma; VHL, Von Hippel-Lindau; SDH, Succinate dehydrogenase; TSC, Tuberous sclerosis complex.

Table 2. Clinical, pathological and follow-up data for our RCC cohort

	Number	Percentage
WHO/ISUP grade*		
1	0	0%
2	29	71%
3	11	27%
4	1	2%
ESRD		
Yes	2	3%
No	66	97%
Pathological T stage		
T1a	36	53%
T1b	11	16%
T2a	4	6%
T2b	8	12%
T3a or greater	5	7%
Unknown	4	6%
Pathological N stage		
N0 or NX	56	82%
N1	8	12%
Unknown	4	6%
Pathological M stage		
M0 or MX	63	93%
M1	3	4%
Unknown	2	3%
Clinical stage		
1	43	63%
2	10	15%
3	10	15%
4	3	4%
Unknown	2	3%
Follow-up		
Mean	5.4 years	
Median	3.0 years	
Range	11 days–28.4 years	
Subsequent metastases		
Yes	5	7%
No	59	87%
Not applicable or unknown	4	6%
Dead of disease		
Yes	6	9%
No	61	90%
Unknown	1	1%

WHO/ISUP, World Health Organisation/International Society of Urological Pathology; RCC, Renal cell carcinoma; ESRD, End-stage renal disease.
*WHO/ISUP grading applicable to clear cell RCC and papillary RCC only.

tubulocystic RCC and ACD-RCC were not identified in this cohort.

The World Health Organisation/International Society of Urological Pathology (WHO/ISUP) grading system was applied to CCRCC and PRCC. Of those tumours (n = 41), 71% (n = 29 of 41) were grade 2, 27% (n = 11 of 41) were grade 3 and 2% (n = one of 41) were grade 4; while CCRCC were more commonly WHO/ISUP grade 2, PRCC was slightly enriched in higher grade cases (Table 2 and Table S1). A history of ESRD was documented in 3% (n = two of 68) of the patients; one patient had VHL-associated CCRCC and the other had TSC-associated RCC as their tumour subtype. Sixty-three per cent of the patients presented with clinical stage 1 disease (n = 43 of 68), 15% stage 2 (n = 10 of 68), 15% stage 3 (n = 10 of 68) and 4% (n = three of 68) stage 4. Three per cent of the cases had unknown clinical stage (n = two of 68). Advanced stage disease (stages 3 and 4) were more commonly seen in Type 2 PRCC (100%, n = one of one) and renal medullary carcinoma (100%, n = one of one), followed by MiT family translocation RCC (78%, n = seven of nine), Type 1 PRCC (40%, n = two of five) and RCC unclassified (25%, n = two of eight).

A large portion of the cohort were patients with a familial kidney cancer syndrome (26%, n = 18 of 68); VHL syndrome-associated RCC accounted for 18% (n = 12 of 68), TSC was associated with 6% of RCC (n = four of 68), while SDH-deficient RCC accounted for 3% (n = two of 68) of the entire cohort. All VHL patients demonstrated renal tumours

with CCRCC morphology and all TSC patients had TSC-associated RCC.

Three patients (4%) had a prior history of chemotherapy (see Table S1) for Wilms' tumour (patient 1), hepatoblastoma (patient 6) and neuroblastoma (patient 25). Of these patients, two developed MiT family translocation RCC (with *TFE3* gene rearrangement) and one had CCRCC.

CLEAR CELL RENAL CELL CARCINOMA

CCRCC was the most common RCC (53%, $n = 35$ of 68) in our cohort (Table 1), with non-VHL-associated CCRCC making up 35% ($n = 23$ of 68) of the cohort and VHL-associated CCRCC 18% ($n = 12$ of 68). The median age for non-VHL RCC patients was 27 years (mean = 25.8, range = 20–30 years), while the median age for VHL-associated RCC patients was 27 years (mean = 26.9, range = 20–30 years. The non-VHL CCRCC showed classic histology (Figure 1A, B). All non-VHL CCRCC tumours were unifocal.

VHL-associated CCRCC often showed classic CCRCC histology similar to sporadic cases (Figure 2A). Many cases ($n =$ eight of 12) however, showed cystic changes (Figure 3A,B), a feature possibly enriched in VHL associated CCRCC. Immunohistochemical assessment of one of these tumours demonstrated patchy CK7 expression (Figure 3C), with a strong/complete membranous carbonic anhydrase IX (CAIX) staining (Figure 3D) and cytokeratin AE1/AE3 staining, supportive of the diagnosis of CCRCC. Seventy-five per cent ($n =$ nine of 12) of VHL-associated CCRCC were multifocal. Germline VHL mutations/rearrangements were confirmed in 75% ($n =$ nine of 12) of VHL patients in the cohort (Table S1); history of germline VHL mutations (testing was not done at our institution) was provided for the remaining three patients.

MIT FAMILY TRANSLOCATION RENAL CELL CARCINOMA

Nine of the 68 tumours (13%) were classified as MiT family translocation RCC based on the presence of previously described morphological, immunophenotypical and cytogenetic features. The median age at presentation was 18 years (mean = 18.1, range = 7–30 years). Seven were transcription factor E3 (*TFE3*) translocated RCC while two were transcription factor EB (*TFEB*) translocated RCC. *TFE3* translocated tumours showed mixed papillary and clear cell features, high-grade nuclei and areas with classic voluminous cytoplasm and bulging distinct cell borders, reminiscent of soap bubbles, as previously described (Figure 4A,B). Other architectural patterns including

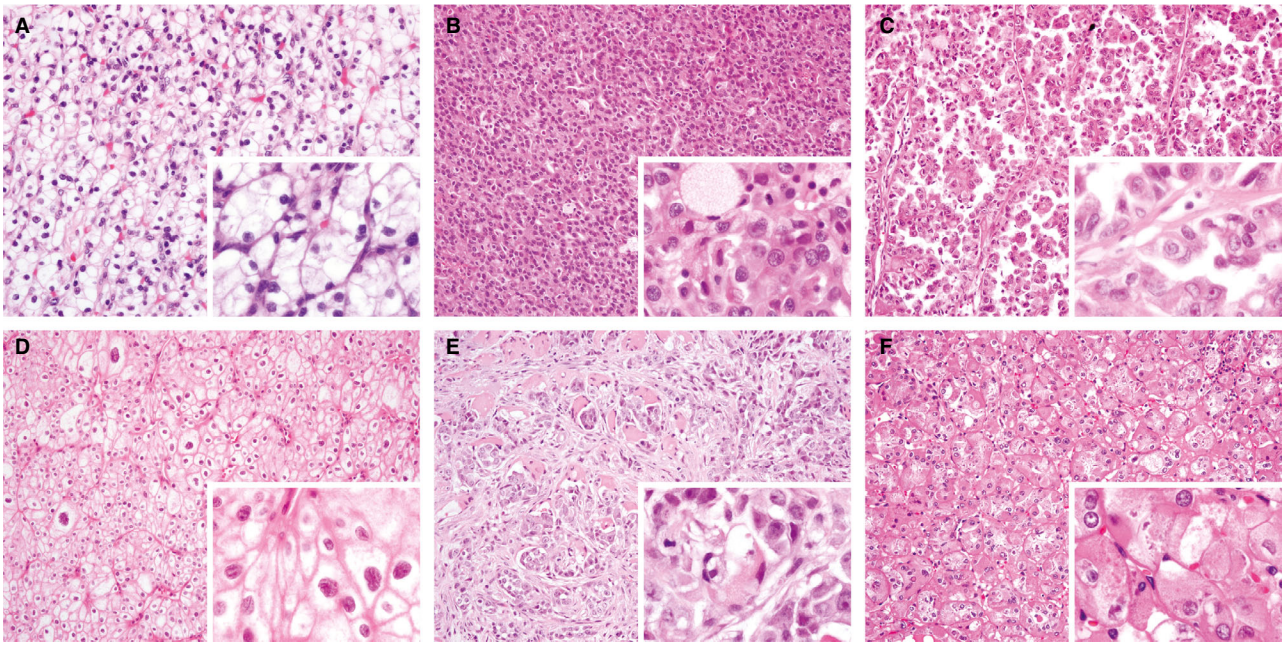

Figure 1. Renal cell carcinoma (RCC) subtypes in our cohort of patients aged 30 years or younger including (**A**, **B**) clear cell RCC (CCRCC), (**C**) papillary RCC (PRCC), (**D**) chromophobe RCC and (**E**) renal medullary carcinoma. In addition, a subset of patients had tumours that could not be further subclassified based on current World Health Organisation (WHO) diagnostic criteria; these tumours were designated RCC, unclassified (**F**). Panel insets show higher magnification to highlight microscopic morphology features.

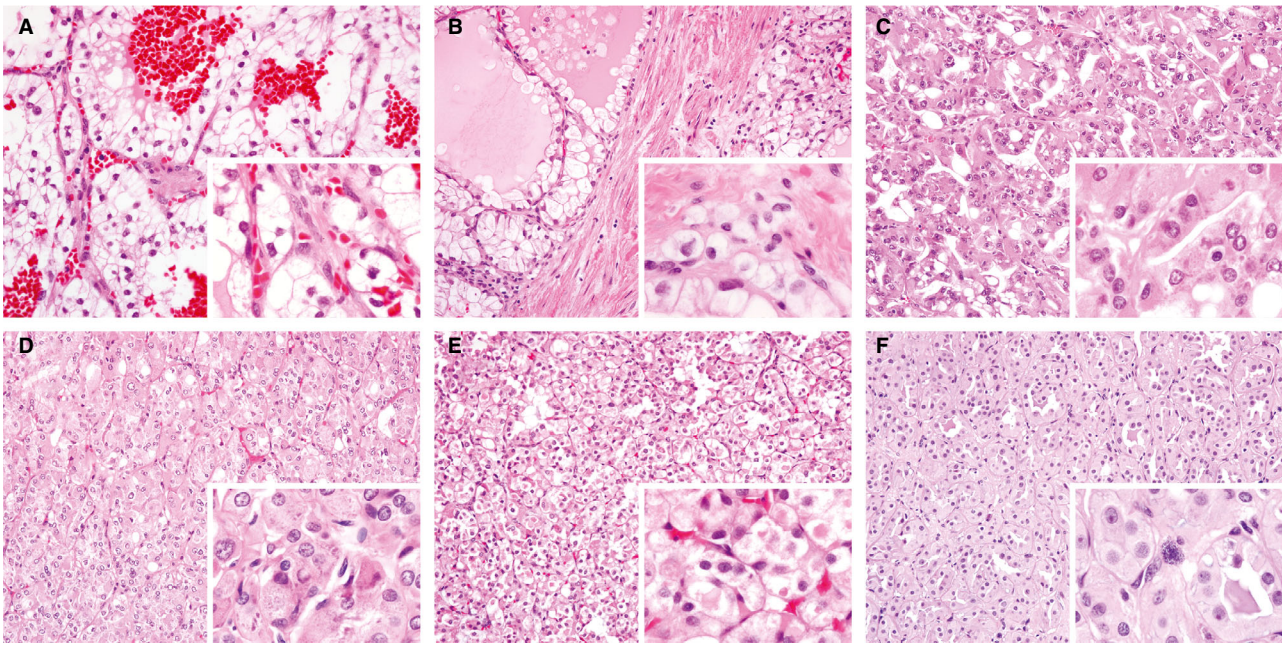

Figure 2. Syndrome-associated renal cell carcinoma (RCC) subtypes in patients aged 30 years or younger. In addition to conventional RCC subtypes, a number of patients had syndrome- associated RCC subtypes, including: (**A**) Von Hippel–Lindau (VHL)-associated clear cell RCC (CCRCC); (**B**) Tuberous sclerosis complex-associated carcinomas resembling renal angiomyoadenomatous tumour (RAT-like) or RCC with smooth muscle stroma; (**C**, **D**) Tuberous sclerosis complex-associated RCC (TSC)-associated carcinomas with a granular eosinophilic histology; (**E**) succinate dehydrogenase-deficient renal cell carcinoma (SDH)-deficient RCC with flocculent eosinophilic inclusions and (**F**) an RCC, unclassified, with oncocytic/morphological features suggestive of FH or SDH; however, this patient did not have any germline pathogenic mutation.

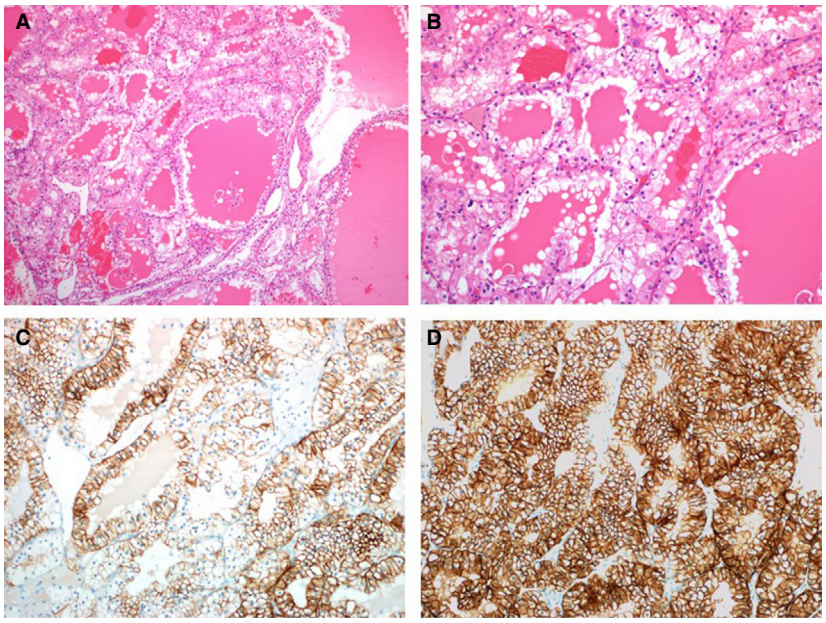

Figure 3. Haematoxylin and eosin (H&E) images showing cystic clear cell RCC (CCRCC) (**A**, **B**) with positive cytokeratin 7 (CK7) (**C**) and carbonic anhydrase IX (CAIX) (**D**) immunostains.

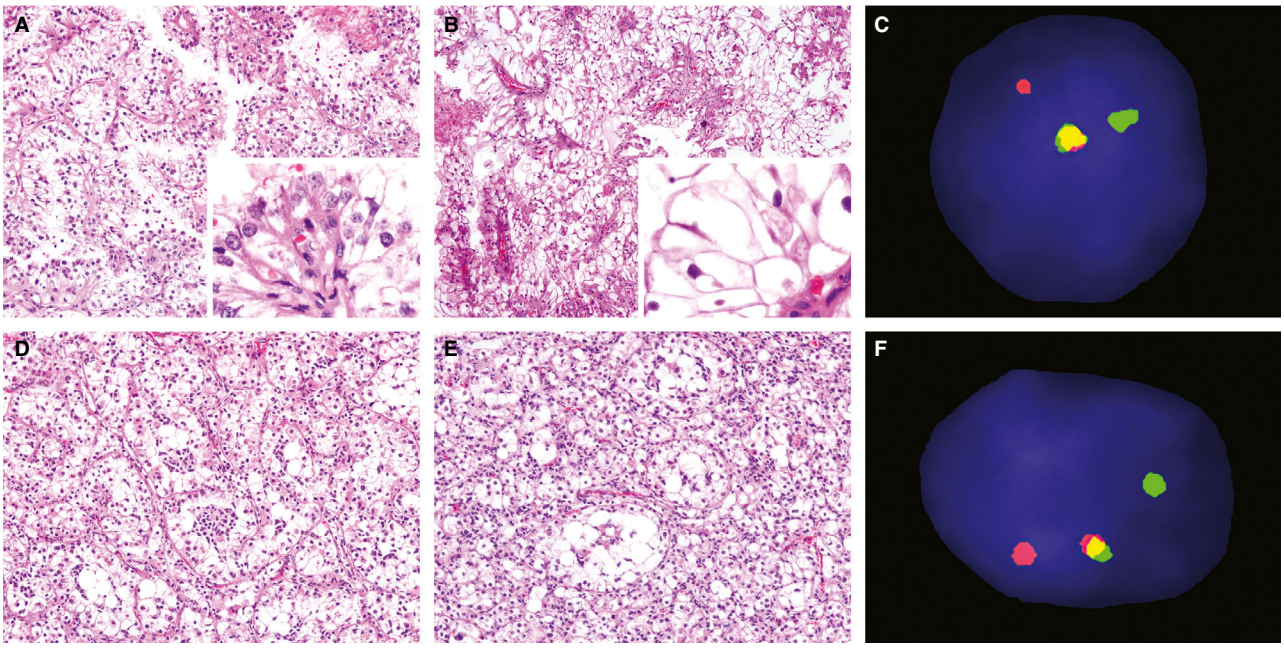

Figure 4. Microphthalmia-associated transcription (MiT) family translocation renal cell carcinoma (RCC) in patients aged 30 years or younger. **A**, **B**, Haematoxylin and eosin (H&E) images demonstrating mixed papillary and clear cell features in two cases of *TFE3* translocated renal cell carcinoma (RCC). Although morphologically suspicious for translocation RCC, these cases were initially designated as RCC, unclassified. Subsequent fluorescence *in situ* (FISH) (**C**) demonstrated *TFE3* gene rearrangements in both cases, confirming the diagnosis. **D**, **E**, H&E images showing the classic 'biphasic' appearance in a case of *TFEB* translocated RCC. Based on morphology alone, this case was highly suspicious for *TFEB* translocated RCC, and subsequent FISH (**F**) confirmed a *TFEB* gene rearrangement. For the FISH images in (**C**) and (**F**), yellow = fusion (wild-type) and red/green = break-apart (rearranged).

solid sheets, trabeculae, and pseudopapillae were also seen. A few of these tumours contained occasional psammoma bodies. Break-apart FISH probe confirmed the presence of *TFE3* translocation in all cases (Figure 4C). *TFEB* translocated tumours exhibited a characteristic biphasic cell population, consisting of large cells with eosinophilic, granular and focally clear cytoplasm and vesicular nuclei with prominent nucleoli admixed with small cells with scant cytoplasm and dense chromatin (Figure 4D,E). These tumours exhibited diffuse expression of at least one marker of melanocytic differentiation (Melan-A or HMB45) (Figure 5C,D). Break-apart FISH probe confirmed the presence of *TFEB* translocation in all cases (Figure 4F). No *TFEB* amplified tumours were seen in this cohort, reflecting that this newly described tumour entity[12,17] was not seen in this younger cohort of patients.

PAPILLARY RENAL CELL CARCINOMA

Six tumours were classified as PRCC based on morphology and immunophenotype. Types 1 and 2 PRCC comprised 7% (five of 68) and 1% (one of 68) of the cohort, respectively. The median age at diagnosis was 22 years (mean = 22.5, range = 16–30 years). Types 1 and 2 tumours showed classical histologic features (Figure 1C). Immunohistochemical staining showed positive CK7 and AMACR expression in all tumours.

CHROMOPHOBE RENAL CELL CARCINOMA

Three cases of ChRCC were identified in our cohort. The median age at diagnosis was 23 years (mean = 24, range = 19–29 years). All tumours demonstrated classic features (Figure 1D). No cases of eosinophilic variant of ChRCC were recognised in this cohort. All tumours demonstrated diffuse CD117 and CK7 expression by immunohistochemistry.

RENAL MEDULLARY CARCINOMA

One renal tumour (1%) in this cohort was consistent with renal medullary carcinoma, diagnosed in a patient with a documented history of sickle cell trait. Histologically, the tumour had classic morphological features including cells with eosinophilic cytoplasm and high nuclear grade arranged in tubular and reticular structures with an infiltrative growth

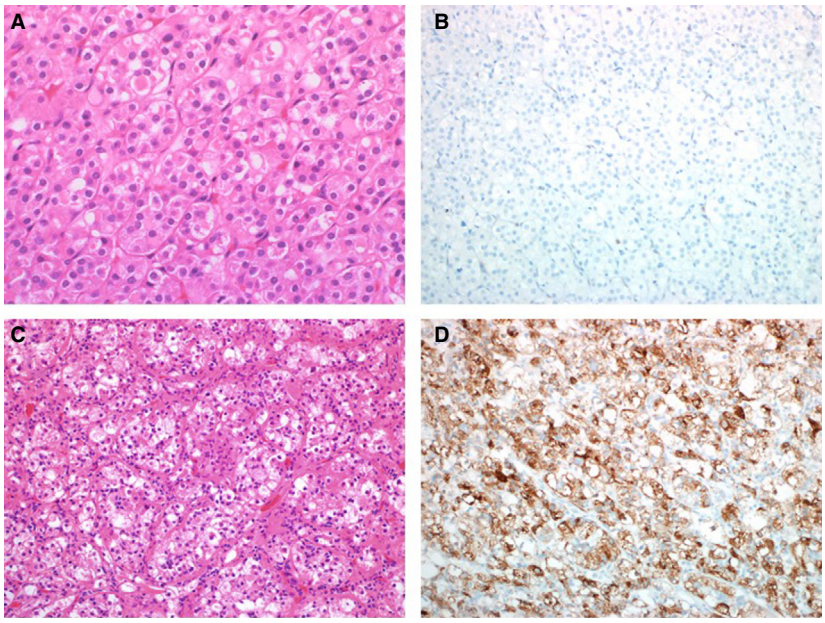

Figure 5. Haematoxylin and eosin (H&E) images showing succinate dehydrogenase-deficient renal cell carcinoma-deficient renal cell carcinoma (RCC) (**A**) with confirmatory immunostain demonstrating loss of succinate dehydrogenase complex iron sulphur subunit B (**B**). H&E images showing the classic 'biphasic' appearance in a case of *TFEB* translocated renal cell carcinoma (RCC) (**C**) showing diffuse melan-A staining (**D**).

pattern, desmoplastic stroma and neutrophilic infiltrate (Figure 1E).

RENAL CELL CARCINOMA ASSOCIATED WITH FAMILIAL CANCER SYNDROMES

Familial cancer syndromes made up 26% (n = 18 of 68) of our cohort. VHL-associated RCC were previously described in the CCRCC section. TSC was associated with 6% (n = four of 68) of RCC in this cohort. The median age at diagnosis was 15 years (mean = 16, range = 7–26 years). Three of the four cases demonstrated granular-eosinophilic macrocystic pattern with papillary architecture (Figure 2C) or nested architecture surrounded by delicate vasculature (Figure 2D). One case demonstrated renal angiomyoadenomatous-like histology (Figure 2B) with nested and cystic clear cells and thick fibromuscular septa. Two tumours were multifocal.

Two cases (3%) had succinate dehydrogenase deficiency syndrome with an associated succinate dehydrogenase complex iron sulphur subunit B-deficient RCC. The patients had a median age of 21 years (mean = 21, range = 13–29 years). Histologically, these tumours were composed of granular, eosinophilic cells arranged in a nested pattern, with characteristic flocculent cytoplasm and eosinophilic inclusions (Figures 2E and 5A). SDHB IHC demonstrated loss of SDHB (Figure 5B), supportive of the diagnosis. All cases demonstrated intact fumarate hydratase (FH) staining.

RENAL CELL CARCINOMA, UNCLASSIFIED

Eight tumours (12%) could not be placed into the well-established renal tumour entities according to the WHO 2016 classification, and hence were placed into the RCC unclassified category (Figures 1F and 2F). The median age at diagnosis for these patients was 23 years (mean = 22.5, range = 16–30 years). Most tumours in this cohort demonstrated features of high-grade tumours with variable architecture (rhabdoid, alveolar, papillary, tubulopapillary, glandular or sarcomatoid) with significant cytological atypia. These tumours could not be classified based on their unusual histological features coupled with negative or variable immunohistochemical and cytogenetic profile. Two tumours had the characteristic morphological features of MiT family translocation RCC; however, evidence of *TFE3*/*TFEB* gene rearrangements could not be demonstrated by FISH evaluation. One tumour was suspicious for SDH-deficient RCC because of its eosinophilic morphology; however, SDHB expression by IHC was intact. Eosinophilic solid

and cystic solid RCC[18] were excluded based upon a lack of classic morphological features coupled with negative CK 20 expression by immunohistochemistry. All cases were seen to exhibit high WHO/ISUP grade (3 or higher).

FOLLOW-UP DATA

The median follow-up period was 3 years (range = 11 days–28.4 years) (Table 2). During the follow-up interval, 7% (n = five of 68) experienced metastasis and 9% (n = six of 68) died of the disease. For patients who died of the disease (Table 3), MiT family translocation RCC was the most common histological diagnosis (68%, n = four of six). Additionally, 50% (n = three of six) of the patients who died of the disease had developed recurrence/metastasis and 83% (n = five of six) had advanced-stage disease.

Table 3. Clinicopathological data for RCC patients who died of disease

	Number	Percentage
Age		
Median (years)	15	
Gender		
Male	3	50%
Female	3	50%
Histological type		
tRCC	4	68%
Medullary RCC	1	16%
RCC, unclassified	1	16%
WHO/ISUP grade		
1	0	0%
2	0	0%
3	4	68%
4	2	32%
VHL		
Yes	0	0%
No	6	100%
Metastasis		
Yes	3	50%
No	3	50%
Clinical stage		
1	1	17%
2	0	0%
3	2	33%
4	3	50%

WHO/ISUP, World Health Organisation/International Society of Urological Pathology; RCC, Renal cell carcinoma; VHL, Von Hippel-Lindau.

Discussion

In children and young adults, RCC is relatively less common than in adults. The morphological classification of adult RCC according to the WHO 2016 criteria has been supported by the detection of specific genetic alterations that distinguish RCCs and their clinical course. In contrast, the rarer RCC in young adults has only recently begun to be better characterised. We have investigated 68 RCC in children and young adults (≤30 years), comprising all RCC from the University of Michigan health system between 1986 and 2018. Speculation remains as to whether or not RCC in younger patients represents a truly different entity from its adult counterpart.[3–5] Our results suggest that RCCs in this age group share many similarities to those in adults, yet possess some distinct clinicopathological characteristics. A gender predominance has not been reported for RCC in children,[19] while in adults, a male predominance has been reported (male:female ratio 2:1)[20]; the male:female ratio in our series was 1:1.

In this study, we sought to explore the applicability of the new 2016 WHO classification to our set of RCCs. We found that CCRCC was the most common subtype in this age group, similar to that reported in the adult population, although at a lower percentage. In several studies of CCRCC in young adults,[19,21,22] CCRCC was reported at frequencies ranging from 6 to 73%. Our series showed a frequency of 53%, which is similar to that reported by Lopez *et al.* (50.7%).[23] Most of the tumours had classic clear cell morphology and low-grade nuclei. VHL-associated CCRCC were commonly found in this cohort, in accordance with previous studies,[13] and were also seen to frequently demonstrate cystic changes and multifocality. None of the VHL-associated CCRCC in this cohort were associated with disease-specific mortality, which reflects the relatively better prognosis associated with such tumours.

MiT family translocation RCC was initially recognised in the 2004 WHO classification as a distinct molecular subtype of RCC with a predilection for paediatric patients, although they are now increasingly being reported in adults.[12,24,25] This subtype represents a significant proportion of RCC in paediatric patients, with widely divergent frequencies reported in recent series (20–75%).[26,27] In our series, MiT family translocation RCC was the second most common subtype, accounting for 13% of our cohort, confirmed by the presence of *TFE3*/*TFEB* gene rearrangements. The biological behaviour of MiT family translocation RCC in children and young adults is controversial. Whereas some series have suggested a good prognosis, others report that prognosis is dependent on the overall stage of tumour and completeness of resection similar to that seen in adult patients.[28] In our series, the majority (seven of nine) of MiT family translocation RCC presented at an advanced-stage disease. The majority also had poor outcomes, with distant metastasis and/or death often occurring years after initial presentation. All MiT family translocation RCC in our cohort who died of the disease had *TFE3* gene rearrangement. Similarly, Xu *et al.*[29] found that compared with non-Xp11.2 translocation RCCs, Xp11.2 translocation RCCs showed a higher tumour grade, advanced pathological stage and poorer cancer-specific survival rates in young adults. Furthermore, all the MIT family translocation RCC in this cohort were related to translocation of *TFE3* and *TFEB* genes, and none of them demonstrated the presence of *TFEB* amplification, which supports the previous observations that this newly described entity is relatively enriched in the older age group patients.[12,17]

Although several previous series of paediatric RCC do not mention any unusual predisposing conditions or underlying syndromes,[30,31] other series[32] report approximately 20–30% of patients with underlying predisposing conditions or syndromes, such as a history of chemotherapy, neuroblastoma, renal failure or tuberous sclerosis. Similarly, in our series RCC associated with familial cancer syndrome or hereditary renal cell carcinoma syndromes accounted for 26% of the cases, although the reported age of presentation of VHL-associated RCC is much younger than that reported in sporadic RCC (mean age of onset 37 versus 61 years) in the majority of the previously published paediatric series.[4,32,33] The median age of VHL-associated RCC patients in our series was 27 years, again confirming that patients with VHL syndromes present with RCC at much younger ages. In addition, we identified SDH-deficient RCC, a subtype that was recently formally recognised in the 2016 WHO classification system, in two patients who were both found to be SDHB-deficient. SDH-deficient RCC occurs in patients with germline mutations in one of the *SDH* subunit genes, although *SDHB* mutation is the most common. Loss of immunohistochemical labelling in SDH-deficient RCC (similar to that seen in our study) reflects the resulting destabilisation of the SDH complex. Histologically, the most distinctive feature is the presence of cytoplasmic vacuoles and inclusion-like spaces containing eosinophilic fluid or flocculent material, which was observed in both of our cases. Furthermore, we identified four cases of RCC developing in the setting of TSC. TSC-associated RCC is known to demonstrate significant heterogeneity with three main histological patterns.[15] Three of our TSC-associated tumours exhibited a granular eosinophilic–macrocystic histology similar to that previously described,[15,34] while one tumour resembled renal angioadenomatous tumour (RAT-like) or RCC with smooth muscle stroma.

Furthermore, three patients had a previous history of exposure to chemotherapy for Wilms' tumour (one patient), hepatoblastoma (one patient) and neuroblastoma (one patient). Of these patients, two developed MiT family translocation RCC, while the third developed CCRCC. These findings support the reported association of approximately 10–15% of translocation RCC with prior exposure to chemotherapy.[35–39] Argani *et al.*[37] described MiT family translocation RCC that arose in young patients who had received chemotherapy. Histologically, these tumours showed typical features described for translocation RCCs. The interval between chemotherapy and the diagnosis of RCC ranged from 4 to 13 years. The apparent predilection of these tumours for children raises the possibility that the relatively increased proliferation that occurs in the growing paediatric kidney may render it more sensitive to the mutagenic effects of several chemotherapies. Falzarno *et al.*[39] also described a higher risk of RCC in younger patients who are survivors of childhood cancers, particularly neuroblastoma. In their study, they observed that in addition to the carcinogenic effects of chemotherapy and or radiation therapy, predisposing underlying genetic conditions and individual susceptibility to therapy side effects may also play a role in the pathogenesis of second malignancies. Almost half the tumours included in their study showed morphological features of MiT family translocation RCC, while the remaining half showed oncocytic cells arranged in tubular and solid architecture. Among RCCs, translocation RCCs have been strongly associated to

exposure to cytotoxic chemotherapy including alkylating agents such as cyclophosphamide and DNA topoisomerase II inhibitors.

Despite applying the new 2016 classification, a high proportion of RCC (12%) in our series remained unclassified. These tumours had a wide variety of architectural pattern, high-grade nuclear features and often eosinophilic morphology. FH and SDHB by IHC in addition to a panel of immunostains as well as cytogenetic studies were inconclusive. A recent study by Li *et al.*[40] reclassified 22 of 33 unclassified RCC in children and young adults that were characterised by predominantly eosinophilic cytoplasm to either SDH-deficient RCC, FH-deficient RCC (HLRCC) or eosinophilic solid and cystic RCC; however, 11 cases (33%) remained unclassified. Pathologists should therefore have a low threshold for performing FH and SDHB IHC when confronted with unclassified eosinophilic RCC in young patients. However, it should be noted that although a renal tumour with FH negative immunophenotype carries a strong correlation with the presence of the FH mutation at the germline level, the type of FH mutation itself may determine whether FH protein loss can be detected by immunohistochemical evaluation. A small subset of patients with HLRCC-associated RCC may demonstrate equivocal results or retain FH expression within the tumour; a correlated finding reported in the literature is that tumours from patients with FH missense mutations may show equivocal or retained FH expression.[41]

Additionally, two tumours that we reported as unclassified RCC had the characteristic morphological findings of MiT family translocation RCC; however, evidence of *TFE3*/*TFEB* gene rearrangements could not be confirmed by FISH evaluation. While break-apart FISH assays for *TFE3* and *TFEB* avoid issues related to polymerase chain reaction (PCR) amplifications and is easier to conduct than reverse transcription–PCR (RT–PCR), false-negative results using common break-apart FISH probes in Xp11 translocation RCC with rare fusions such as *RBM10–TFE3* or *NONO–TFE3* fusions has been reported and should be considered.[42]

Finally, clear cell papillary RCC, recognised as a distinct entity in the new 2016 WHO classification, was not seen in our cohort; however, this entity has previously been described in young adults. Lopez *et al.*[23] reported that 9.3% of their RCC series in patients aged 40 years or younger showed clear cell papillary histology.

Although we note the limitations of our study, namely a retrospective review, it is one of the largest series to date addressing the spectrum of RCCs in children and young adults, according the recent 2016 WHO classification of renal tumours.

In summary, we describe the morphological, immunophenotypical and molecular spectrum of RCC in patients aged 30 years or younger. Our results suggest that RCC in children and young adults is a relatively uncommon disease that shares many histological similarities to RCC occurring in adults and yet demonstrates some unique clinicopathological differences. MiT family translocation RCC and rare familial syndrome subtypes are relatively more frequent in the paediatric and adolescent age groups than in adults. CCRCC is less frequent than in adults; however, it accounted for the most common subtype seen in this age group. MiT family translocation RCC patients presented with advanced-stage disease and had poor clinical outcomes. The large and heterogeneous subgroup of unclassified RCC contains phenotypically distinct tumours with further potential for future subcategorisation.

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Conflicts of interest

All authors have no relevant disclosures.

Author contribution

Eman Abdulfatah: analyzed the data and wrote the manuscript (first author); J M Kennedy: collected the data; K Hafez: provided clinical and follow up data; M S Davenport: provided clinical and follow up data; H Xia: provided clinical and follow up data; A Z Weizer: provided clinical and follow up data; G S Palapattu: provided clinical and follow up data; TMM Morgan: provided clinical and follow up data; R Mannan: analyzed the data; X-M Wang: Analyzed the data; S M Dhanasekaran: provided clinical and follow up data; S D Kaffenberger: provided clinical and follow up data; DE Spratt: provided clinical and follow up data; L Kunju: analyzed pathological data; A Wu: analyzed pathological data; M Lew: analyzed pathological data; A M Udager: analyzed pathological data and revised the manuscript; A M Chinnaiyan: mentor, supervised and revised the manuscript; R Mehra: mentor, supervised and revised the manuscript (Corresponding and senior author).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinicopathologic data for 68 RCCs in patients 30 years of age or younger