DEPARTMENT OF PATHOLOGY

Pathology e-gazette

Volume 1 Issue 3 August 2022

New WHO classification of renal cell tumor: what the clinician needs to know

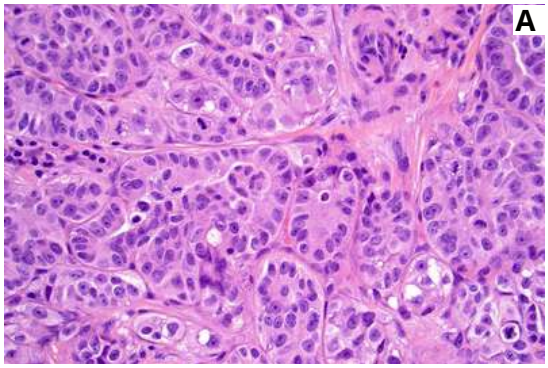
- The most recent World Health Organization (WHO) classification of renal neoplasms accounts for more than 50 entities and provisional entities.
- Newly recognized epithelial renal tumours in the 2016 WHO classification are **HLRCC associated RCC, SDH deficient RCC, tubulocystic RCC, acquired cystic RCC, and clear cell papillary RCC .**

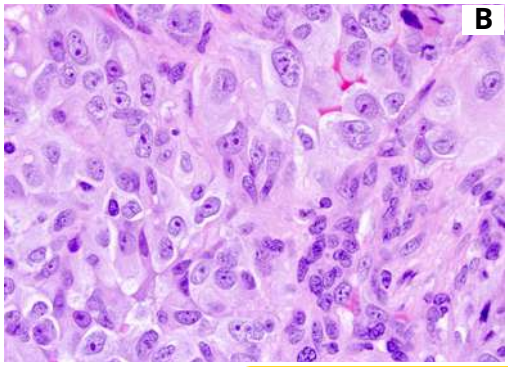
Emerging or provisional renal tumour entities

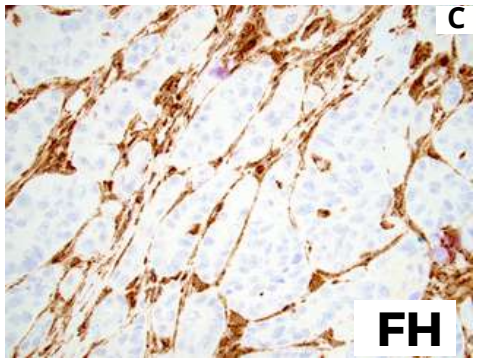
- The 2016 WHO classification includes some rare entities, not yet well characterized in terms of morphology, immunohistochemical stain and genetic features, therefore placed under the category "emerging/provisional tumors". These entities are **thyroid-like follicular RCC, RCCs associated with ALK gene rearrangement, Renal cell carcinoma with (angio) leiomyomatous stroma and TCEB1 mutated RCC.**

1. Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome-associated renal cell carcinoma/ FH-deficient RCC

- Patients with HLRCC syndrome usually present with cutaneous leiomyomas and in female uterine leiomyoma and less frequently leiomyosarcomas
- papillary growth pattern and large nucleus with prominent eosinophilic nucleolus with perinuclear halo, which is the hallmark of these neoplasms
- Loss of Fumarate Hydratatse (FH) expression (Germline FH mutations)
- S-2(2-succino)-cysteine (2SC) (strong and diffuse nuclear and cytoplasmic stain)

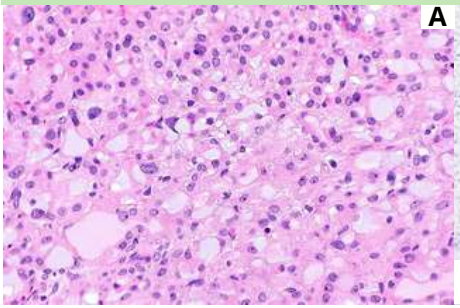


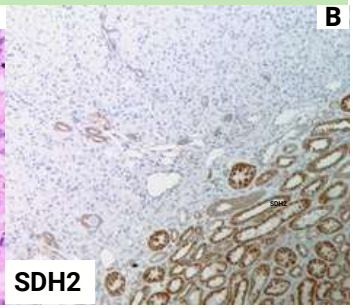




2. Succinate dehydrogenase deficient neoplasia

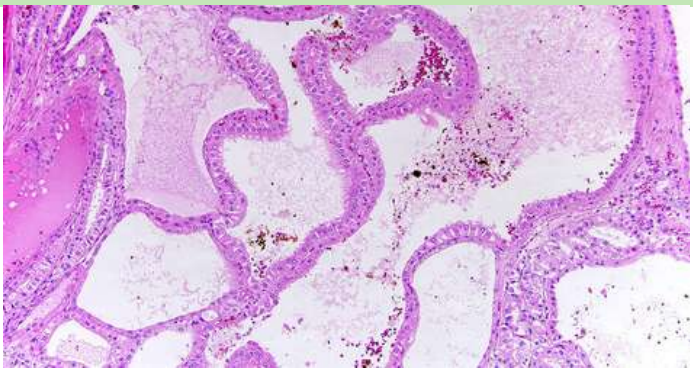
- **Defined by the double-hit inactivation of one of the SDH genes (SDHA, SDHB, SDHC, SDHD, and SDHAF2)**
- **The majority of the cases have loss of SDHB gene identifiable by IHC.**
- **They are typically solitary masses, multifocal and bilateral in 30% of patients.**





3. Tubulocystic RCC

- **Strong prevalence in males (male/female ratio of 7:1) and higher incidence in the fifth and sixth decade. Most of the tumors are cystic and in pT1 stage and behave in an indolent fashion. Only rare cases presented metastasis to the pelvic lymph nodes, bone, liver and peritoneum.**



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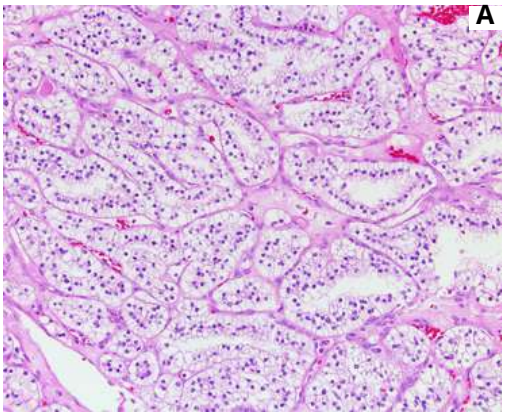
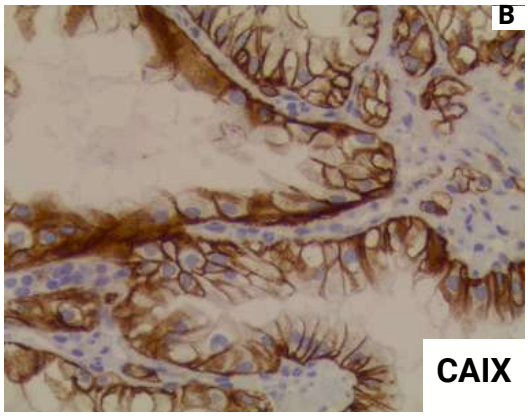
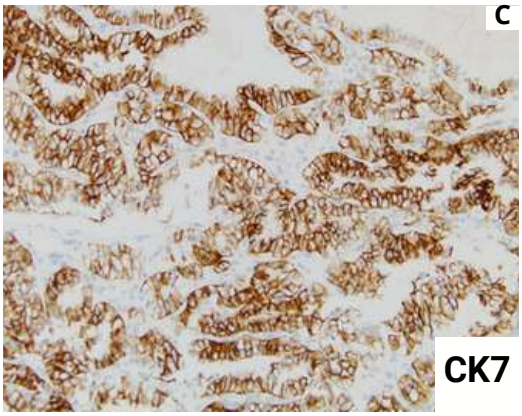
4. Clear cell papillary RCC





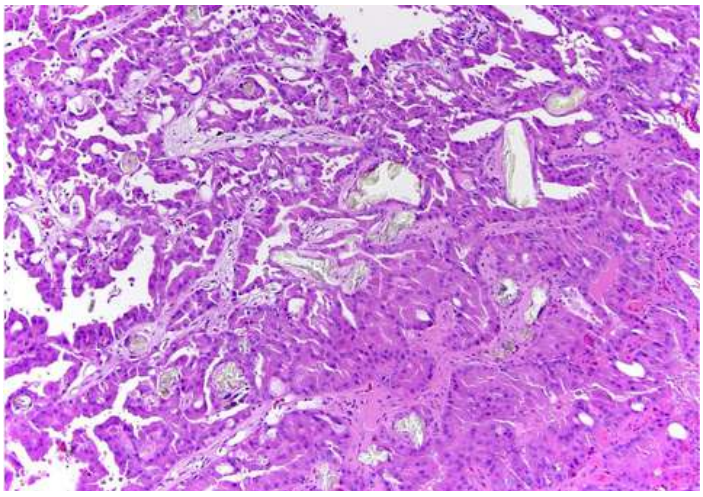


- Mixture of tubular, cystic, acinar and papillary patterns
- Lined by a single layer of cuboidal to low columnar cells
- Scant eosinophilic to clear cytoplasm
- Nuclei apical to mid-cytoplasmic orientation

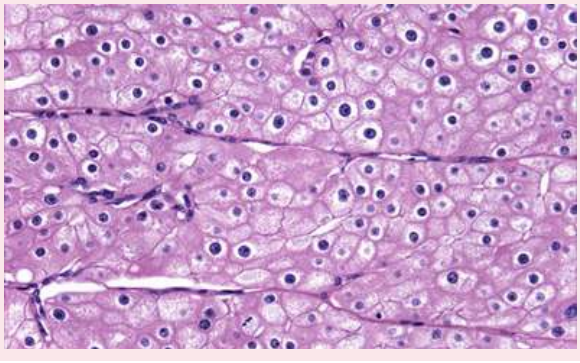
- The characteristic immunoprofile with diffuse cytokeratin 7 staining, GATA3 positivity, "cup-shaped" carbonic anhydrase IX staining distribution, and negative results for AMACR and CD10, along with the absence of VHL alterations in almost all tumor, distinguish this entity from ccRCC and papillary RCC.

5. Acquired cystic disease-associated renal cell carcinoma (ACD-RCC)

- ACD-RCC is specific for the cystic disease condition and occurs only in end-stage renal disease patients, but patients with ACD can develop also other RCC histotypes.
- The vast majority of ACD-RCC present intratumoral calcium oxalate deposition in the luminal structures and in the stroma.
- These tumors have been usually detected at an early stage, thus the clinical course is usually indolent.



QUIZ TIME



Which of the following is the most likely IHC profile of the renal neoplasm shown in image?

(A) CK7+, KIT+, vimentin-, CAIX-
(B) CK7+, KIT+, vimentin-, CAIX+
(C) CK7-, KIT+, vimentin-, CAIX-
(D) CK7-, KIT-, vimentin+, CAIX+
(E) CK7+, KIT+, vimentin+, CAIX-

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Renal cell tumors and new described entities grouped according to their cellular features/architectural pattern, anatomic location, associated diseases, and genetic alterations

Cellular features and/or Architectural pattern	Anatomic location	Associated diseases	Genetic alterations
Clear Cell RCC	Renal medullary carcinomas	Acquired cystic disease-associated RCC	TCEB1 RCC
Papillary RCC	Collecting duct carcinomas	RCC in neuroblastoma survivors	MiT family translocation RCC
Chromophobe RCC			FH deficient RCC
RCC with (angio) leiomyomatous stroma			ALK Rearrangement-associated RCC
Clear cell papillary RCC			SDH-deficient neoplasia
Biphasic squamoid papillary RCC			
Mucinous tubular spindle cell carcinoma			
HOT/LOT			
Eosinophilic solid and cystic RCC			
Tubulocystic RCC			
Thyroid like follicular RCC			
Papillary renal neoplasm with reverse polarity			

Immunohistochemical profile for Renal cell carcinoma with clear cell features

	CK7	CD10	CA-IX	Keratins / EMA	Melanocytic Markers	TFEB / TPF3
Clear Cell RCC	-	+	+ (diffuse)	+	-	-
Clear Cell Papillary RCC	+	-	+ (basal cup-like)	+	-	-
Multilocular cystic renal cell neoplasm of LMP	-	+	+	+	-	-
MiTF translocation-associated RCC	-	+	-	- (weak to neg	+/-	+

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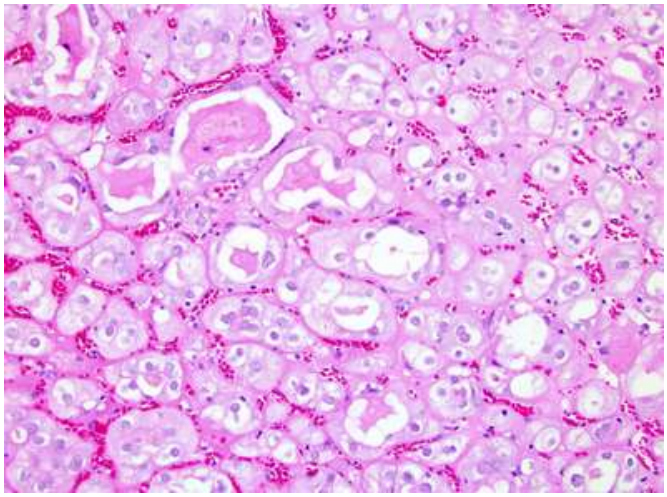
Emerging or provisional renal tumour entities

- The 2016 WHO classification includes some rare entities, not yet well characterized in terms of morphology, immunohistochemical stain and genetic features, therefore placed under the category “emerging/provisional tumors”.

1. Thyroid like follicular RCC



Cimadamore A, Cheng L, Scarpelli M, Massari F, Mollica V, Santoni M, Lopez-Beltran A, Montironi R, Moch H. Towards a new WHO classification of renal cell tumor: what the clinician needs to know-a narrative review. Transl Androl Urol. 2021 Mar;10(3):1506-1520.

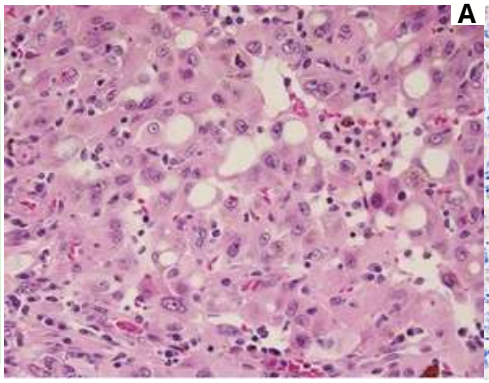
- **Characterized by structures resembling thyroid follicles with accumulation of inspissated colloid-like material that closely mimic a well-differentiated thyroid follicular neoplasms.**
- **The main differential diagnosis are a chronic pyelonephritis or metastatic thyroid carcinoma.**

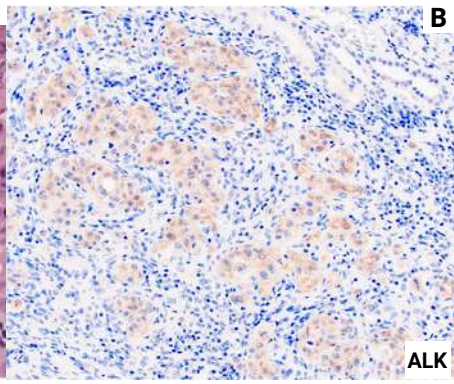
2. Renal cell carcinoma with (angio) leiomyomatous stroma (RCCLMS)

These rare tumors are constituted by two admixed components, epithelial—usually nest/tubules/papillary structure of clear cell, with low grade nuclei—and stromal—non-neoplastic leiomyomatous or fibroleiomyomatous

3. Anaplastic lymphoma kinase (ALK) Rearrangement associated RCC (ALK-RCC)

- **Mucinous background, intracytoplasmic mucin and myxoid changes can be a helpful clue to recognize these rare tumor eligible for a potential targetable therapy.**
- **Definitive diagnosis can only be done by performing IHC for ALK antibody and FISH analysis for ALK rearrangement.**





4. TCEB1 Renal cell carcinoma

- **A small fraction of wt-VHL RCC are characterized by inactivation of the TCEB1 gene that encodes for a protein part of the E3 ubiquitin ligase complex. This entity resembles ccRCC, express CAIX as well, present thick fibromuscular bands transecting the tumor and clear cell cytology with voluminous cytoplasm.**

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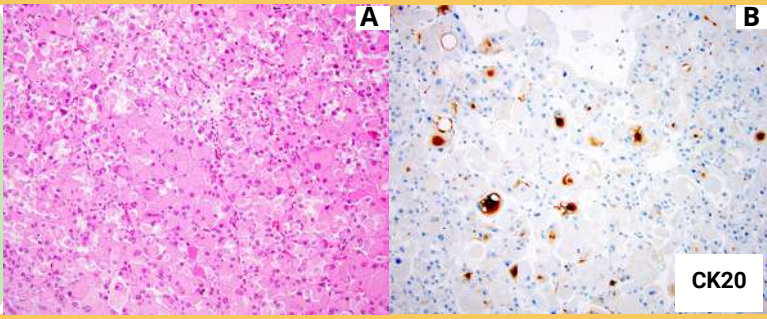
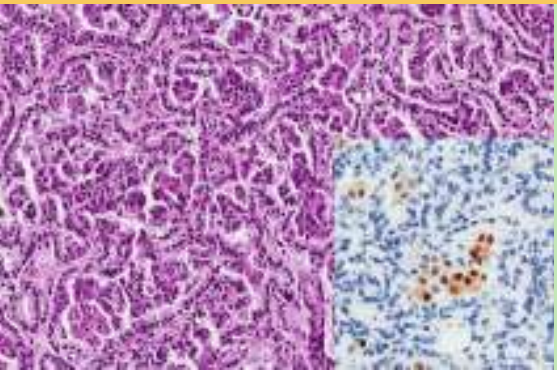
Recommendations for the next WHO classification

1. Eosinophilic solid and cystic RCC (ESC RCC)

- Solid and cystic architecture, voluminous eosinophilic cytoplasm, granular cytoplasmic stippling, CK20 positivity either diffuse or focal are the typical features of these tumors.
- Next generation sequencing analysis and karyotype profiling evidenced that ESC-RCC are characterized by somatic tuberous sclerosis gene mutations (TSC1 and TSC2) in the great majority of cases.



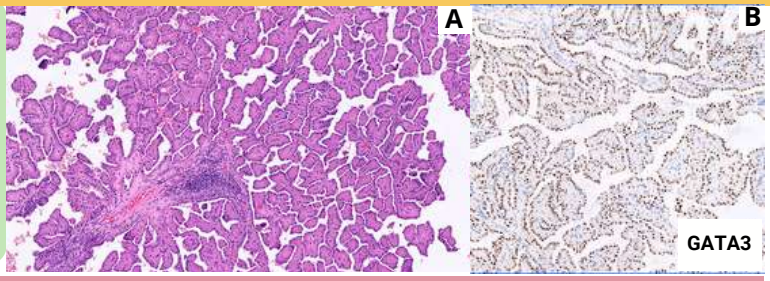
2. Biphasic squamoid papillary RCC



This new entity may represent a distinct subtype of papillary RCC type 1, on the basis of the morphological, IHC and molecular similarities.
This tumour have two cell populations:
1) larger eosinophilic cells with abundant cytoplasm and higher-grade nuclei designated as 'squamoid' (squamous cell-like), organized in glomeruloid or micronodular formations resembling alveolar structures
2) A population of smaller cells with amphophilic or clear and scant cytoplasm, admixed with the larger cells.
Insert image shows BCL1 IHC stained squamoid cells

3. Papillary renal neoplasm with reverse polarity (PRNRP)

- These tumors are characterized by low-grade nuclear features, inverted nuclear location, eosinophilic cytoplasm, branching papillae with thin fibrovascular cores.
- They are characteristically positive for GATA3 and L1CAM and the great majority of them harbors recurrent mutation of KRAS.



WHO/ISUP grading system for clear cell and papillary renal cell carcinomas

Grade	Findings
1	Nucleoli are absent or inconspicuous and basophilic at 400x magnification
2	Nucleoli are conspicuous and eosinophilic at 400x and visible but not prominent at 100x
3	Nucleoli are conspicuous and eosinophilic at 100x
4	Extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation

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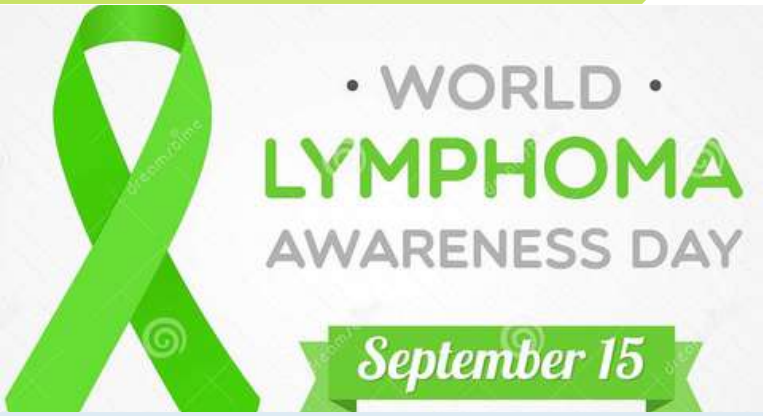
Take Home Message

- Many clinically useful entities with distinct morphological and molecular features have been introduced & few are also under active research which may be included in future classifications.
- The accurate identification of these recently classified tumors with the help of ancillary techniques and genetic analysis will improve patient's stratification and therapy and may have an impact on their families in the specific case of a genetic syndrome-associated RCC.

Answer to the Quiz :

Answer is *(A)*

The image shown is chromophobe renal cell carcinoma (ChRCC), eosinophilic variant. The immunoprofile of ChRCC is typically CK7+, KIT+, vimentin- and CAIX-



World Lymphoma Awareness Day (WLAD) was initiated in 2004 to raise public awareness of both Hodgkin and non-Hodgkin lymphoma in terms of symptom recognition, early diagnosis and treatment. It is a global initiative hosted by the Lymphoma Coalition (LC), a non-profit network organisation of 83 lymphoma patient groups from 52 countries around the world.

Message from the Department

"You don't make progress by standing on the sidelines, whimpering and complaining. You make progress by implementing ideas"

Dr. Garima Anandani
Dr. Tarang Patel
Dr. Gyanendra Singh

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