New and emerging eosinophilic (pink) renal tumors

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Pink renal tumors are in fashion!
Some pink renal tumors are rare, some not so rare!

- Oncocytoma
- Chromophobe RCC (eosinophilic)
- Clear cell RCC ('pink')
- Papillary RCC (oncocytic)
- Epithelioid AML
- MiTF RCC
- SDH deficient RCC

Major diagnostic dilemma!
Why study rare tumors?

Only pathologists can do this!

Figuring out rare tumors can help understand common tumors

Entities may emerge with distinct clinical and other features (hereditary/syndromic association)

Direct benefit to patients (prognosis, treatment)

Drs. D Huntsman and D. Klimstra
Why study rare tumors?

Morphology of distinct neoplasms may explain molecular changes (understand disease process of cancer!)

New techniques can be tested and applied

H&E can be diagnostic!

Pathologists seem to like it!

Drs. D Huntsman and D. Klimstra
Emerging/provisional entities

Succinate dehydrogenase (SDH) deficient RCC

Thyroid-like follicular RCC

ALK translocation RCC
Clear cell renal cell carcinoma
Multilocular clear cell renal cell neoplasm of low malignant potential
Papillary renal cell carcinoma
  Type 1
  Type 2
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
MiT family translocation renal cell carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease associated renal cell carcinoma
Clear cell papillary/tubulopapillary renal cell carcinoma
Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
Succinate dehydrogenase (SDH) deficient renal carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Renal oncocytoma
Succinate dehydrogenase (SDH) deficient RCC

1-9. Succinate dehydrogenase–deficient renal carcinoma
45 y/o male, “pink” tumor, looks “funny”!
SDH deficient RCC (oncocytoma like, solid growth, focal cysts)
SDH deficient RCC (intracytoplasmic vacuoles)
SDH deficient RCC – fluffy cytoplasm!
SDHB IHC: effective screening for SDH mutation
<table>
<thead>
<tr>
<th></th>
<th>SDH deficient RCC</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-CK</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>C-kit</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PAX-8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SDHB</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>
SDH mitochondrial complex

Diagram showing the SDH complex within the mitochondrial inner membrane. The complex involves enzymes SDHA, SDHB, SDHC, and SDHD. The electron transport chain includes CoQ, Cytochrome C (Cyt C), and enzymes IV and V. The Krebs cycle involves succinate and fumarate. ATP production is shown as ADP → ATP.
Succinate Dehydrogenase (SDH)-deficient Renal Carcinoma: A Morphologically Distinct Entity

A Clinicopathologic Series of 36 Tumors From 27 Patients

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Angela Chou, FRCPA, † † † Julie Paik, MBBS,** † Roderick J. Clifton-Bligh, PhD, FRACP, † † †
Bruce G. Robinson, MD, FRCPA,† † † Diana E. Benn, PhD,** † † Kirsten Hills, FRCPA,∥
Fiona Maclean, FRCPA,‖ Nicola D. Niemeijer, MD,∥∥
Lilijana Vlatkovic, MD,*** Arndt Hartmann, MD,# Eleonora P. M. Corssmit, MD,∥∥
Geert J. L. H. van Leenders, MD,PhD,∥ Christopher Przybycin, MD,† † †
Jesse K. McKenney, MD,† † † Cristina Magi-Galluzzi, MD,PhD,† † † Ashi Yilmaz, MD,† † †
Darryl Yu, MD,*,† † † Katherine D. Nicoll, FRCPA,‖ ‖ Jim L. Yong, FRCPA,||
Mathilde Stbny, MD, PhD,∥∥ Evgeny Yakirevich, MD, DSc,‖ ‖ Stewart Fleming, MD,
FRCPATH,‖ ‖ ‖ Chung W. Chow, FRCPA,**** Markku Miettinen, MD,† † † †
Michal Michal, MD,§ and Kiril Trpkov, MD,† † † †
SDH deficient neoplasia

- PHEO/PGL syndrome type 4
- SDH mutated PGL
- SDH deficient GIST
- SDH deficient pituitary adenoma

All are SDHB negative by IHC

= mutated mitochondrial complex 2

Gill AJ. Histopathology 2018; 72, 106-116
SDH deficient RCC –
36 tumors from 27 patients

Younger adults
Age 37y (range 14-76y)

“Oncocytoma-like”

Solid or nested growth

Flocculent cytoplasm,
Often low grade nuclei,
Intracytoplasmic vacuoles,
Focal cysts

C-kit, panCK, CK7 = typically negative!

Vimentin mostly neg. (some pos.)

SDHB negative on IHC

Dysfunction of the mitochondrial complex 2

SDH germline mutation

Most indolent, 1/3 aggressive!
High grade transformation in SDH deficient RCC!!!
High grade transformation in SDH deficient RCC!!!
ISUP Vancouver Classification of Renal Neoplasia 2012
Emerging/provisional entities

Succinate dehydrogenase (SDH) deficient RCC

*Thyroid-like follicular RCC*

*ALK translocation RCC*
Thyroid-like follicular RCC

Resembles thyroid follicular carcinoma, but doesn’t stain like one (r/o MS!)
Thyroid-like follicular RCC?

MS from thyroid ca!

Thyroglobulin

PAX8

TTF1
Thyroid-like follicular RCC with spindle cell/sarcomatoid differentiation
Thyroid-like follicular RCC

About 40 cases reported

Mostly females, broad age range

IHC: PAX8+, CK7+
Thyroglobulin-/TTF1 –

Molecular: limited data
Variable gains and losses

Usually non-aggressive, rare cases with MS
ALK-rearrangement RCC

*ALK* translocation and *ALK* protein expression

*ALK* break apart probe (FISH)  ALK protein expression (IHC)
Renal medullary carcinoma-like morphology (pediatric, sickle cell trait)

VCL-ALK rearrangement RCC

TPM3-ALK rearrangement RCC
ALK-rearrangement RCC

Adult ones show variable morphology – with mucin (no sickle cell trait!)

ALK-STRN rearrangement RCC
ALK-rearrangement RCC

**ALK-ETL4** rearrangement - tubulopapillary morphology – **NO mucin!**
ALK-rearrangement RCC

About 30 cases reported
Children, young adults, 50-60y

Prognosis – some good, some not so good
MS disease at presentation – 6 patients
3/18 patients with F/U died

Potential Tx with ALK inhibitors!

IHC:
CK7, 34βE12, AMACR, Vimentin, all + ALK+

Molecular – different ALK partners:
VCL
TPM3
ETL4
STRN
HOOK1
CLIP1
KIF5B
KIAA1217

Kuroda N et al. USCAP 2019
Pink renal tumors are found everywhere!

Pathology is Nice!
Emerging entities:

SDH deficient RCC

Thyroid-like follicular RCC

ALK translocation RCC

Anything else after 2016?

“ESC”

“HOT”

“LOT”

Three letter *pink* tumors!
53 y/o female, 6 cm solid-cystic mass
Pink, solid and cystic (macro- and micro- )
Hobnal cell lining, variable thickness of septae
Diffuse eosinophilic (pink) growth
Cytoplasmic ‘stippling’ (coarse granularity)!!!
Cytoplasmic coarse granularity ('stippling')!!!
Diagnosis

Pink (eosinophilic) renal tumor (solid and cystic?)

Differential Diagnosis:

- Oncocytoma
- Chromophobe RCC (eosinophilic)
- Epithelioid AML
- Papillary RCC (oncocytic)
- Clear cell RCC (‘pink’)
- MiT RCC
- SDH deficient RCC
16 RCC sporadic in non-TSC patients; can also occur in pt. with TSC

Eosinophilic Solid and Cystic (ESC) RCC

All in females, indolent clinical course!
Gross features

Solid-cystic or solid

Great majority females

90% sporadic, no TSC!

Single tumors (most)
CK20 positive, CK7 negative profile
Eosinophilic Solid and Cystic Renal Cell Carcinoma (ESC RCC)

Further Morphologic and Molecular Characterization of ESC RCC as a Distinct Entity

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Gabriella Nesi, MD,§ Eva Comperat, MD,∥ Mathilde Sibony, MD,¶ Adeboye O. Osunkoya, MD,§
Ming Zhou, MD, PhD,** Neriman Gokden, MD,†† Xavier Leroy, MD,‡‡ Daniel M. Berney, MD,§§
Isabela Werneck Cunha, MD, PhD,∥∥ Maria L. Musto, MD,¶¶ Daniel A. Athanazio, MD,###
Aslı Yılmaz, MD,* Bryan Donnelly, MD,*** Eric Hyndman, MD,*** Anthony J. Gill, MD, PhD,†††
Jesse K. McKenney, MD,‡‡‡ and Tarek A. Bismar, MD*

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**TABLE 2.** Enriched Gene Sets and Pathways in Genomic Altered Regions in ESC RCC

<table>
<thead>
<tr>
<th>Enrichment Score</th>
<th>Pathway Term</th>
<th>Genes</th>
<th>P</th>
<th>FDR (%)</th>
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<tbody>
<tr>
<td>25.9</td>
<td>Regulation of TOR signaling pathway</td>
<td>AKT1S1, MLST8, TSC1, TSC2</td>
<td>&lt; 0.001</td>
<td>0.7</td>
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<tr>
<td>15.6</td>
<td>Tyrosine-specific protein kinase</td>
<td>AXL, TEK, EGFR, IINSR, MET, NTRK2, ROR2, SYK</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td>15.1</td>
<td>Cell cycle control</td>
<td>CCNE1, CDK6, CDKN2A, CDKN2B, RB1</td>
<td>&lt; 0.001</td>
<td>0.4</td>
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<tr>
<td>14.98</td>
<td>Smoothened signaling pathway</td>
<td>GLI3, HIPK2, PTCH1, SMO</td>
<td>0.002</td>
<td>3.76</td>
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<tr>
<td>9.2</td>
<td>Induction of apoptosis by intracellular signals</td>
<td>BCL3, BBC3, BAX, JAK2, ABL1, HIPK2, XPA</td>
<td>&lt; 0.001</td>
<td>0.17</td>
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</tbody>
</table>

FDR indicates false-discovery rate.
Platinum Priority – Kidney Cancer

Editorial by Pedram Argani on pp. 487–488 of this issue

Somatic Bi-allelic Loss of TSC Genes in Eosinophilic Solid and Cystic Renal Cell Carcinoma

Rohit Mehra\textsuperscript{a,b,c,†}, Pankaj Vats\textsuperscript{a,c,d,†}, Xuhong Cao\textsuperscript{c,e}, Fengyun Su\textsuperscript{a,c}, Nicole D. Lee\textsuperscript{c}, Robert Lonigro\textsuperscript{a,c}, Kumpati Premkumar\textsuperscript{c,e}, Kiril Trpkov\textsuperscript{f}, Jesse K. McKenney\textsuperscript{g}, Saravana M. Dhanasekaran\textsuperscript{a,c,†}, Arul M. Chinnaiyan\textsuperscript{a,b,c,e,†, *}

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<tr>
<th>TSC2</th>
<th>RC_1087</th>
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<th>RC_1150</th>
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<th>RC_1088</th>
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<td>Fs_In</td>
<td>Nonsense</td>
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</table>
| Fs_Del: Frameshift deletion; Fs_In: Frameshift insertion; LOH: Loss of heterozygosity}
Eosinophilic Solid and Cystic (ESC) RCC

Summary

Novel tumor with mostly indolent behaviour

Characteristic morphology, IHC (CK20+/CK7-)

TSC1 and TSC2 bi-allelic mutation

Great majority females with sporadic tumors

Mostly solitary tumors

Two patients described post-neuroblastoma
ESC RCC - all you need to know!

Females
TSC and non-TSC
CK20
Good prognosis

J McKenney™
Oncocytic (pink) “hybrid” tumors

Heterogeneous tumors with overlapping features (oncocytoma and ChrRCC) in Birt-Hogg-Dubé Sy, renal oncocytosis or sporadic

Usually CD117+ and CK7+/-

Diagnostic ‘gold standard’:
  Morphology?
  IHC?
  Special stains?
  EM?
  Cytogenticics or molecular?
Low-grade Oncocytic Tumor (LOT) (CD117 Negative, Cytokeratin 7 Positive)

Oncocytoma? ChrRCC? Or else?

CD117 CK7
Low-grade oncocytic tumour of kidney (CD117-negative, cytokeratin 7-positive): a distinct entity?

Kiril Trpkov, Sean R Williamson, Yuan Gao, Petr Martinek, Liang Cheng, Ankur R Sangoi, Asli Yilmaz, Cheng Wang, Pilar San Miguel Fraile, Delia M Perez Montiel, Stela Bulimbasi, Joanna Rogala & Ondrej Hes

1 University of Calgary and Calgary Laboratory Services, Calgary, AB, Canada, 2 School of Medicine, Henry Ford Health System and Wayne State University, Detroit, MI, USA, 3 Charles University and University Hospital Pilsen, Pilsen, Czech Republic, 4 Indiana University School of Medicine, Indianapolis, IN, 5 El Camino Hospital, Mountain View, CA, USA, 6 QEII Health Sciences Centre and Dalhousie University, Halifax, NS, Canada, 7 Hospital Álvaro Cunqueiro, Vigo (Pontevedra), Spain, 8 Institute Nacional de Cancerología, Mexico City, Mexico, 9 University Hospital Center, Zagreb, Croatia, and 10 Regional Specialist Hospital, Wroclaw, Poland
Gross morphology

Size 30 mm (median); range 11 – 135 mm; all single tumors
Clinical features and Follow-up

Older individuals
M : F = 1 : 1.9

Stage:
pt1a-b (90%)

Follow-up:
All alive - NOD
median 23.5 mo (mean 41)
(range: 3 to 118 mo)
Lack of capsule, diffuse solid and tubular growth
Solid and vague nested growth
“Oncocytoma-like” areas, compact nests
“Chromophobe-like” areas, compact nests
Trabecular and reticular growth
Edematous areas with loosely arranged cells
Edematous areas with loosely arranged cells
Immunohistochemistry

CD117 negative, CK7 positive profile
Array CGH (7 cases)

Deletions:

19p33.3 (7/7)

1p36.33 (5/7)

No other consistent chromosomal gains or losses

Ongoing additional studies
Low-grade Oncocytic Tumor (LOT)
CD117 Negative, Cytokeratin 7 Positive

Summary
Remarkably consistent morphology and immunoprofile

Does not fit completely either oncocytoma or ChrRCC

Uniform loss of 19p33.3 and frequent loss of 1p36.33, but no other losses or gains

Needs more study – possibly a distinct entity?
Oncocytoma

ChrRCC
Oncocytoma

ChrRCC
Parking “LOT” for weird “pink” tumors!

Oncocytoma

ChrRCC
High-grade Oncocytic Tumor (HOT) of Kidney
High-grade Oncocytic Tumor (HOT)

Pink

Cytoplasmic vacuoles
High-grade Oncocytic Tumor (HOT)

Pink cytoplasm

Cytoplasmic vacuoles
High-grade Oncocytic Tumor (HOT)

**IHC positive:**
- CD117 (9/14)
- CD10 (12/13)
- **Cathepsin K (13/14)**
- PAX8, AE1/AE3, SDHB

**IHC negative:**
- CK7 (rare cells)
- TFE3, HMB45, Melan A

No TFE3 & TFEB rearrangements

Indolent behavior!
High-grade Oncocytic Tumor (HOT) of Kidney

“High-grade oncocytic renal tumor”: morphologic, immunohistochemical, and molecular genetic study of 14 cases

Huiying He¹ · Kiril Trpkov² · Petr Martinek³ · Ozlem Tanas Isikci⁴ · Cristina Maggi-Galuzzi⁵ · Reza Alaghehbandan⁶ · Anthony J Gill⁷,⁸,⁹ · Maria Tretiakova¹⁰ · Jose Ignacio Lopez¹¹ · Sean R. Williamson¹² · Delia Perez Montiel¹³ · Maris Sperga¹⁴ · Eva Comperat¹⁵ · Fadi Brimo¹⁶ · Ali Yilmaz² · Kristyna Pivovarcikova³ · Kveta Michalova³ · David Slouka¹⁷ · Kristyna Prochazkova¹⁸ · Milan Hora¹⁸ · Michael Bonert¹⁹ · Michal Michal³ · Ondrej Hes³

Virchows Arch. 2018;473(6):725-738

Another emerging renal entity - not in the WHO!
High-grade Oncocytic Tumor (HOT) in TSC patient

Histopathology 2019; 75: 440–442.
High-grade Oncocytic Tumor (HOT) in TSC patient
New and emerging pink renal tumors

**SDH-deficient RCC**
“Onco with fluffy/vacuolated cytoplasm, Ckit neg, SDHB neg”

**HOT**
“Oncocytoma on steroids, Cathepsin K”

**Thyroid-like follicular RCC**
“Rule out MS thyroid Ca”

**LOT**
“Parking LOT Onco-ChrRCC, Ckit neg/CK7 pos”

**ALK-rearrangement RCC**
“Multiple patterns (mucin), ALK pos”

**ESC RCC**
“Females, solid-cystic, coarse cytoplasm, CK20 pos”
REVIEW

New and emerging renal entities: a perspective post-WHO 2016 classification

Kiril Trpkov¹ & Ondřej Hes²
¹University of Calgary and Calgary Laboratory Services, Calgary, Alberta, Canada
²University Hospital Pilsen, Pilsen, Czech Republic

Trpkov K & Hes O
Thank you
Somatic Mutations of TSC2 or MTOR Characterize a Morphologically Distinct Subset of Sporadic Renal Cell Carcinoma With Eosinophilic and Vacuolated Cytoplasm

Ying-Bei Chen, MD, PhD, Leili Mirsadraei, MD, Gowtham Jayakumaran, MS, Hikmat A. Al-Ahmadie, MD, Samson W. Fine, MD, Amuradha Gopalan, MD, S. Joseph Sirintrapun, MD, Satish K. Tickoo, MD, and Victor E. Reuter, MD
“Sporadic Renal Cell Carcinoma With Eosinophilic and Vacuolated Cytoplasm” = “HOT” (but with a name than no one can remember!)

It is not “sporadic” always – but it is a real entity!