Guest Speakers:

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Basel Seminars 2013: Handout

1. M.B. Amin: Update on the pathology standards for bladder cancer   
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2. M.B. Amin: Pseudoneoplastic mimics of bladder cancer   
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3. M.B. Amin: Role of immunohistochemistry in diagnostic surgical pathology of the urinary bladder   
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4. I.S. Roberts: Kidney – tubulointerstitial lesions   
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7. H. Moch: Common challenges in kidney cancer   
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UPDATE ON PATHOLOGY STANDARDS FOR BLADDER CANCER

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BASIC OVERVIEW
Molecular Pathways for Bladder Cancer Oncogenesis

**PAPILLARY PATHWAY**

- Normal Urothelium
- 9q/-9p-
- Urothelial Hyperplasia
- LG URCa
- HRAS/FGFR3, PIK3CA-Akt
- Recurrence (70%)

**NON--PAPILLARY PATHWAY**

- 9q/-9p-
- Dysplasia/CIS
- P53, Rb, 8p-8p+, 17p-
- HG URCa
- E-cad, MMP, VEGF, COX2
- Invasive URCa
- MMP9, VEGF, TSP, IL8, EGFR, IMP3, LAMC2
- Metastasis (~50%)
UROTHELIAL NEOPLASMS

CLINICIANS PERSPECTIVE

"Superficial"

Non-invasive

Lam. Prop. invasive (pT₁)

Urothelial CIS

"Muscle Invasive"

Invasive papillary carcinoma (pT₂+)

Invasive carcinoma

"Superficial"

"Muscle Invasive"
UROTHELIAL NEOPLASMS

“Superficial”
- “Chronic”
  - Recur (new occurrences)
- Over time
  - Different areas of bladder
- Conservative management
- Generally good prognosis

“Invasive tumors”
- “Aggressive”
  - Invade wall of bladder, may cause metastasis
- More radical treatment
- Poor prognosis

PATHOLOGIC STAGE

HISTOLOGIC GRADE
Papilloma—papillary carcinoma

Invasive papillary carcinoma

Flat noninvasive carcinoma

Flat invasive carcinoma
Updated Protocol for the Examination of Specimens From Patients With Carcinoma of the Urinary Bladder, Ureter, and Renal Pelvis

Mahul B. Amin, MD; John R. Srigley, MD; David J. Grignon, MD; Victor E. Reuter, MD; Peter A. Humphrey, MD, PhD; Michael B. Cohen, MD; M. Elizabeth H. Hammond, MD; for the Members of the Cancer Committee, College of American Pathologists

PROTOCOLS & GUIDELINES FOR REPORTING BLADDER CANCER

cap.org (2012)

Protocol for the Examination of Specimens From Patients With Carcinoma of the Urinary Bladder

Protocol applies primarily to invasive carcinomas and/or associated epithelial lesions, including carcinoma in situ.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
- Bladder Biopsy, Transurethral Resection of Bladder Tumor (TURBT) Specimen
- Cystectomy (Partial, Total)
  - Radical Cystoprostatectomy
  - Pelvic Exenteration

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For the Members of the Cancer Committee, College of American Pathologists

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Review – Bladder Cancer

ICUD-EAU International Consultation on Bladder Cancer 2012: Pathology

Mahul B. Amin², Jesse K. McKenney², Gladell P. Paner³, Donna E. Hansel⁴, David J. Grignon⁵, Rodolfo Montironi⁶, Oscar Lin⁶, Mercè Jorda⁶, Lawrence C. Jenkins⁷, Mark Soloway⁷, Jonathan L. Epstein⁷, Victor E. Reuter⁸

Eur Urol 2013

European Association of Urology
What’s New in the 2012 Consensus Offering?: An Update on:

- The **knowledge of the histoanatomy** of the bladder as it pertains to the diagnosis and staging of bladder cancer
- The **prognostic significance of histologic grading by the WHO (2004)/ISUP system**, its contributions, shortfalls and opportunities for refinement
- The **information needed from the clinicians by the pathologist** in order to provide optimal pathologic reporting of bladder cancer
- On **nomenclature for inverted lesions** of the bladder

35 Urologic Pathologists from 13 Countries
What’s New in the 2012 Consensus Offering?: An Update on:

- The histologic types of bladder cancer and the variants of urothelial cancer, some relatively recently described, with a focus on definition for diagnosis and their implied clinico-pathologic significance

- Role of immunohistochemistry and molecular studies in contemporary routine practice diagnosis, prognostication or prediction of bladder cancer

- The reporting of bladder cancer in transurethral resection of bladder tumors (TURBT) and cystectomy specimens
Reporting of Bladder Cancer

- **Guidelines**: CAP and European Society of Uropathology etc.
- Reporting in **synoptic pattern** is preferred
- **Clinical information** important for pathology diagnosis
  - Cystoscopic impression
  - Previous history of bladder cancer
  - Previous history of therapy (intravesical or systemic)
  - History of stones, indwelling, catheter, etc.
- A deeper bite for assessment of MP involvement in TURBTs should be preferably submitted separately, for larger tumors
# REPORTING ELEMENTS IN BLADDER CANCER

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>Biopsy, TURBT, cystectomy</th>
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<tbody>
<tr>
<td>HISTOLOGIC TYPE</td>
<td>Uca or variant</td>
</tr>
<tr>
<td>SUPERFICIAL LESIONS</td>
<td>Dysplasia &amp; in situ lesions</td>
</tr>
<tr>
<td>HISTOLOGIC GRADE</td>
<td>W.H.O./ISUP 2004</td>
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<tr>
<td>MUSCULARIS PROPRIA</td>
<td>Present , absent, indeterminant</td>
</tr>
<tr>
<td>ANGIOLYMPHATIC INVASION</td>
<td>Present , absent, indeterminant</td>
</tr>
<tr>
<td>DEPTH OF INVASION</td>
<td>For in situ &amp; invasive lesions</td>
</tr>
<tr>
<td>PATHOLOGIC STAGE</td>
<td>AJCC/UICC pTNM system</td>
</tr>
<tr>
<td>MARGIN STATUS</td>
<td>In cystectomy specimens</td>
</tr>
</tbody>
</table>
Urothelial denudation

- Seen with instrumentation with CIS
- Extensive or complete denudation in a bladder biopsy should be reported as correlation with concurrent cytology results may yield a positive diagnosis of malignancy in the patient
Urothelial hyperplasia

- Papillary or flat
- Thickened urothelium without cytologic atypia
- Flat hyperplasia may be seen adjacent to low grade papillary tumors
- Papillary hyperplasia is suggested to be a precursor lesion for a subset of papillary urothelial neoplasms
Squamous Metaplasia

- Should be reported and specified whether keratinizing or not and whether focal or multifocal
- Current evidence does not support any precursor potential with focal changes, although multifocal and/or extensive lesions precede or may be associated concurrent with neoplasia
Glandular Metaplasia

- Cystitis cystica & cystitis cystica glandularis are proliferative lesions
  - They may be associated with intestinal metaplasia

Glandular metaplasia is not a risk factor for adenocarcinoma or UCa

- Multifocal disease
- Metaplasia with dysplastic changes
  - Associated with risk for adenocarcinoma
GRADING OF UROTHELIAL LESIONS

- Flat lesions
- Papillary lesions
- Inverted lesions
- Invasive lesions
WHO (2004)/ISUP Grading System

Flat Lesions:
- Normal
- Hyperplasia
- Reactive
- Dysplasia
- CIS
- Atypia of unknown significance

Papillary Lesions:
- Non invasive
  - Papilloma
  - PUNLMP
  - Low grade
  - High grade
- Invasive
  - High grade
  - Low grade (rare)

Inverted Lesions:
- Non invasive
  - Papilloma
  - PUNLMP
  - Low grade
  - High grade
- Invasive
  - High grade
Urothelial Dysplasia

- Overall features are those of a neoplastic atypia but which fall short of the criteria for CIS; dysplasia is not further graded.
- There is some evidence, largely genetic, that dysplasia shares some abnormalities with CIS and therefore likely represents a precursor lesion.
- Few studies, most dated, indicate a 5-19% risk of developing cancer.
Urothelial Dysplasia

• The diagnosis of de novo dysplasia (i.e. in a patient without history of bladder neoplasia) should not be made or should be made with great caution as the vast majority of patients, in the limited studies, do not progress to cancer.

• While dysplasia likely represents a marker of urothelial genetic instability, the diagnosis should not by itself invoke any therapy; continued surveillance is recommended.
Urothelial CIS

- Biologically, therapeutically and prognostically significant flat lesion
- There is a spectrum of nuclear and architectural atypia. CIS defined by WHO (2004) / ISUP includes cases diagnosed previously as severe dysplasia and even some cases previously diagnosed as moderate dysplasia
- Development of invasion is seen in 20 to 30% of the cases
ATYPIA OF UNKNOWN SIGNIFICANCE (WHO/ISUP)

- Cases with inflammation, severity of atypia out of proportion to extent of inflammation - cannot rule out dysplasia
- Subtle “mild” nuclear alterations not categorically reactive or dysplastic
- *Comment to urologist*: Recommend follow-up after inflammation subsides
Grading of Urothelial Carcinoma

- The non-invasive urothelial lesions and neoplasms can be flat, papillary (exophytic) and inverted (endophytic). All 3 growth patterns may be seen in a single tumor.

- The World Health Organization (WHO) (2004) / International Society of Urologic Pathologists (ISUP) classification system is the recommended system. It has also been endorsed by the WHO 2004 Blue Book, the 4th Series Armed Forces Institutes of Pathology Fascicle on Bladder and the 7th edition AJCC Cancer Staging Manual.
LOW GRADE
Inverted Neoplasms

- Papillary tumors may be associated with a variable degree of inverted growth patterns; although focal areas of inverted growth are not uncommon, prominent or exclusive inverted growth is much rarer and when encountered may pose problems related to grading or assessment of invasion.

- From the clinical standpoint during cystoscopy, inverted tumors made be polypoid, dome-shaped or frequently raise the suspicion of invasive urothelial carcinoma.
Exophytic tumor  Inverted tumor

Courtesy R. Montironi, Italy
Inverted High Grade without invasion

Inverted High Grade with invasion
INVERTED PAPILLOMA

Papillary tumor

Inverted papilloma
Inverted Papilloma
Inverted PUNLMP
### WHO (2004) / ISUP: Prognostic Significance

<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>LG pap ca</th>
<th>HG pap ca</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence</strong></td>
<td>9-18</td>
<td>17-62</td>
<td>34-78</td>
<td>34-74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(34)</td>
<td>(50)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>2%</td>
<td>11</td>
<td>7-12</td>
<td>-</td>
</tr>
<tr>
<td><strong>progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>0</td>
<td>0-4</td>
<td>3-18</td>
<td>27-61</td>
</tr>
<tr>
<td><strong>progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>100</td>
<td>93-100</td>
<td>82-96</td>
<td>65-90</td>
</tr>
</tbody>
</table>

- Does not predict risk at individual patient level
- Need for incorporation with other clinical parameters in nomograms to provide personalize risk stratification
Grading of bladder cancer in Europe

- W.H.O./ISUP 2004 (51%)
- W.H.O. 1973 (43%)
- W.H.O. 1999 (31%)

Some practices provide 2 grading systems
Contributions of WHO (2004) /ISUP

- Establishment of uniform terminology and common definitions for papillary neoplasms
- Establishment of detailed criteria of various preneoplastic conditions and various grades of tumor
- Correlation with urine cytology terminology, facilitating cyto-histologic correlation and making it easier for urologists to manage patients
- Creation of a category of tumor that identifies a tumor with a negligible risk of progression (PUNLMP), whereby patients avoid the label of having cancer which has psychosocial and financial implications. Neither is a benign lesion (papilloma) diagnosed in these patients, so they may still be followed up closely
Contributions of WHO (2004) /ISUP

- Identification of a distinct group of patients (high-grade papillary UCa) who would be ideal candidates for intravesical therapy
- Removal of ambiguity in diagnostic categories in WHO 1973 system (e.g., TCC grade 1-2, TCC grade 2-3)
- Stratification of bladder tumors into prognostically significant categories
- Emergence of molecular correlates for high grade tumors and tumors at the low-grade end of the spectrum which may help provide ancillary grading tools, and possibly guide in future refinements of the current grading system
Handling grade heterogeneity in bladder cancer
Grading Papillary Urothelial Neoplasm with Histologic Heterogeneity

- Grade heterogeneity is not uncommonly encountered in papillary urothelial neoplasia.
- There are studies showing that pure HG papillary UCa has a higher disease progression rate than tumors with mixed high-grade and low-grade areas.
- The WHO (2004)/ISUP system recommends grading of heterogeneous tumors to be based on the highest grade present in a tumor.
Grading Papillary Urothelial Neoplasm with Histologic Heterogeneity

• There is no current widely acceptable definition or criteria to provide quantitative estimate of size of smallest focus required to “upgrade” a lesion.

• Studies are needed to establish quantitative/semi-quantitative criteria that need to be present to alter assignment of grade in tumors with grade heterogeneity
Grading Papillary Urothelial Neoplasm with Histologic Heterogeneity

- The distinction between PUMLMP and low grade papillary U Ca is not that critical in an individual patient
- Distinction of low grade from high grade carcinoma is more important
- When assigning the tumor grade in tumors with borderline grade histology, other tumor parameters such as multifocality, previous grade of the tumor, size of lesions, frequency of recurrence, presence of concurrent CIS, positive cytology may be factored in the grading
- Currently, no reliable or acceptable IHC or molecular markers to assist in grading
Papillary Hyperplasia with Cytologic Atypia

• Terminology used when criteria of papillary neoplasia are not fulfilled but there is a background of cytologic atypia
  • Dysplasia with early papillary formations
  • CIS with early papillary formations

• Usually occurs in the backdrop of treatment setting

• These terms are only descriptive diagnoses and outcome studies are not available
CIS with early papillary features
Dysplasia with early papillary features
pT1 – invasion into the lamina propria
67-75% 5-year survival

pT2 – invasion into the m. propria
60-63% 5-year survival

pT3 – invasion into the perivesical fat
31-50% 5-year survival

pT4 – invasion of adjacent organs
10-25% 5 year survival
Grading Invasive Cancer

Practice in the United States

- Almost all cases, once diagnosed as invasive, are called high grade.
- Exceptionally rare cases are called low grade including variants such as nested variants.
- Most studies show that once invasive, depth of invasion is more important.
Grading Invasive Cancer

- **Practice in the Europe**
  - Further grading of high grade (WHO 2004/ISUP system)
  - *G2 and G3 categories (of WHO 1973 system)*
  - Incorporated into algorithms such as the EORTC system
  - Criteria for distinction of G2 versus G3 not well defined but studies show prognostic significance in at least pT1 tumors
- 2 types of muscle - awareness important for pT staging

LP inv. (M. mucosae) - pT1
M. propria inv. - pT2
Standard: For patients with lamina propria invasion (T1) but without MP in the specimen, repeat resection should be performed prior to additional intravesical therapy.

http://www.auanet.org/guidelines/
Muscularis Mucosae Muscle

- **Hyperplastic Muscularis Mucosae:**
  - Patterns frequently observed but exceed thickness of previously described MM

- **To avoid confusion in diagnosis, documentation of “MM-only invasion” by carcinoma is not recommended in the main pathologic diagnosis, and should be reported as “urothelial carcinoma with lamina propria invasion (at least pT1)”**

- **Involvement of MM may be included in a comment to provide information on depth/extent of invasion**
M. mucosaeae muscle pattern - typical

Wispy or thin muscle bundles, 71/150 (47%)
M. mucosae muscle patterns

Typical
Wispy or thin muscle bundles

Variant
Hypertrophic MM muscle
M. mucosae muscle pattern

Hypertrophic – Haphazard (33%)
M. mucosae muscle pattern

Hypertrophic – M. propria-like (45%)
Typical Hypertrophic-Haphazard

Hypertrophic-M. propria-like
Muscularis Propria

• Several terms are currently being used to describe both MP (deep muscle, muscle proper or detrusor muscle) and MM (superficial muscle). These terms are not recommended and use of standardized nomenclature of “MP muscle bundles” is recommended.

• It is important to document the presence or absence of MP in a biopsy irrespective of involvement.

• Some institutions recommend not mentioning the presence or absence of MP in low grade tumors and require documentation in high grade tumors only.
Muscularis Propria

- In cystectomy specimens, a more objective and reproducible anatomical or extent of disease criterion is needed between pT2a and pT2b subcategories.

- Substaging of pT2 disease and recognition of pT3 disease is not tenable in TURBT specimens.
Muscle Involved by UCa, Indeterminate Type

- Muscle bundles indeterminate between MM and MP should be reported with terminology such as "invasive urothelial carcinoma with invasion of muscle, indeterminate type" to prompt the urologist for a restaging biopsy procedure.
Adipose Tissue

• Adipose tissue is frequently present in the LP and MP of the urinary bladder, usually scant in the former and abundant in the latter.
• Involvement of adipose tissue by tumor in biopsy or TURBT specimens should not be automatically interpreted as pT3 disease.
• There is limited reliability of pT3a vs pT3b subcategorization as gross involvement of perivesical fat (extravesical fat) may not always be readily recognizable and may be mimicked by reactive changes.
Assessment of pT2 vs. pT3 – cystectomy alone
Lamina Propria Invasion

• There are problems with interobserver reproducibility in the diagnosis of early LP invasion

• When early invasive urothelial carcinoma is suspected, diagnosis through examinational of additional levels, or in a consensus manner either with other pathology colleagues or thru quality assurance meeting is encouraged
Microinvasive Urothelial Carcinoma

• To diagnose early invasion, stringent criteria such as: only focal invasion, less than 1 high power field, or 0.5 mm from the nearest basement membrane, should ideally be employed.

• Studies are needed to establish a clinically significant definition of microinvasive urothelial carcinoma. Until there is understanding of the definition, it is recommended that only stringent criteria be used or the term microinvasive carcinoma not be used.
Minimal (micro) invasion
Substratification or Substaging of Lamina Propria Invasion (pT1)

• Depth of invasion may be established either:
  • Up to MM: pT1a or beyond the MM or vascular plexus: pT1b;
  • Up to MM: pT1a, in to MM: pT1b, or beyond the MM or vascular plexus: pT1c

• Currently substaging is not recommended due to the lack of widely accepted and reproducible criteria although there is much need for such studies

• It is recommended for the pathologist to provide an estimate of the LP invasion in pT1 tumors with respect to depth and/or quantity of invasion (e.g. focal, multifocal, extensive, etc.)
Reporting Extent of Lamina Propria Invasion

• Some estimate as extent of invasion must be provided
• No specific further recommendations
• Extent in mm (difficult in many TURBT & multifocal disease)
• “Substaging” currently not recommended
Extensive invasion
VASCULAR-LYMPHATIC INVASION - PROGNOSIS

- Precise prognosis remains controversial, as many cases are “overcalled”
- Vascular invasion – correlated with LN and systemic mets
- Must be strictly defined before diagnosed – may be used to determine need for adjuvant therapy
Retraction a mimic of vascular-lymphatic invasion
Use Strict Criteria

IHC not necessary to confirm this feature
Vascular Lymphatic Invasion (LVI)

- Shariat et al – 4,257 patients
  - pT1 – 11%, pT2 – 31%, pT3 – 52%, pT4 – 61%
- 30-50% of cystectomy specimens – correlates with high stage & node positivity
- LVI not associated as an independent predictor in many studies
- LVI likely significant in node negative disease
## Histologic Variants of Bladder Cancer

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Therapy:</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive</td>
<td>Sarcomatoid Ca</td>
<td>Nested variant</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>Small cell</td>
<td>UCa with small tubules</td>
</tr>
<tr>
<td>Small cell</td>
<td>Large cell neuroendocrine</td>
<td>Plasmacytoid UCa</td>
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<tr>
<td>Sarcomatoid</td>
<td>Lymphoepithelioma-like</td>
<td>UCa with clear cell features</td>
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<td>Signet ring adenocarcinoma</td>
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<tr>
<td>Giant cell carcinoma</td>
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<tr>
<td>Favorable</td>
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<td>Pure LELC</td>
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<td>Verrucous Ca</td>
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<td>Carcinoid tumor</td>
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BLADDER PATHOLOGY

At US & Canadian Academy of Pathology Meeting
Baltimore 2013

Mahul B. Amin, MD
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Kiril Trpkov, MD
David J. Grignon, MD
pT0 disease

- No evidence of primary carcinoma at cystectomy following prior cancer diagnosis TURBT
- Incidence in series – 5-20%
- Incidence on the increase as “early” radical cystectomy offered to high risk for progression patients
  - Refractory & multifocal CIS
  - High grade pT1 disease
  - Multiple recurrent high grade tumors +/- CIS
- Entire previous biopsy site should be sampled
- Patients with pT0 disease have a more favorable outcome than those with pT2 disease at cystectomy
Lymph node involvement:

- Approx. 10-15% of cystectomy specimens
- LN (+): median survival – 23 months
- LN (-): median survival – 63 months

- Minimum number of lymph nodes in cystectomy not established
- Size of largest metastatic focus and extranodal extension, if present should be documented
- *Frozen section is not an optimal method for a primary diagnosis of invasive urothelial carcinoma or to perform pathologic staging prior to a cystectomy*
Lymph Node Dissection & Analysis

- Manual lymph node dissection is key
- Submitting all fat or dissecting LNs after Carnoy’s fixative shows marginal clinical benefit
- All grossly dissected LN tissue should be entirely submitted except in positive lymph nodes where representative section may be submitted

Reporting
  - Number of positive LNs & number examined
  - Location - primary (true pelvis) vs secondary (common iliac LNs)
THE BEST BLADDER CANCER PATHOLOGY STANDARDS

• A Pathologist who integrates the gross and microscopic findings and judiciously employs ancillary tools (IHC et al) in the context of the clinical history to make a “diagnosis” for patient management.

• A Urologist (“the treating hand”) who works closely with the Pathologist (“the guiding hand”) in the care of their patients.
Thank you!!!
PSEUDONEOPLASTIC MIMICS OF BLADDER CANCER

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Pseudoneoplastic mimics of bladder cancer

Mimics of CIS
- Reactive atypia
- Radiation atypia
- Polyoma virus infection

Mimics of Papillary Neoplasia
- Papillary/polypoid cystitis
- Nephrogenic adenoma
- Avulsion and pseudopapillary artifacts

Mimics of Invasive Cancer
- Inflammatory lesions (malakoplakia, amyloidosis)
- Pseudocarcinomatous hyperplasia
- Von Brunn’s nests
- Cystitis cystica & glandularis +/- intestinal metaplasia
- Nephrogenic adenoma
- Mullerianosis
- Paraganglia
- Ectopic prostate tissue
- Post operative spindle cell nodule
EMPHYSEMATOUS & BULLOUS CYSTITIS
EMPHYSEMATOUS & BULLOUS CYSTITIS
MALAKOPLAKIA
NORMAL PARAGANGLIONIC TISSUE
REACTIVE ATYPIA

History of stones, inflammation, instrumentation, therapy

General monotony, maintained polarity

Nucleomegaly, prominent nucleoli

Minimal to absent nuclear contour & chromatin irregularities

Accompanying inflammation in lamina propria or in the mucosa
FLAT LESIONS WITH ATYPIA
PROBLEMS AND PITFALLS

Inflammatory atypia: Nucleomegaly, mitoses, prominent nucleoli

Caution in interpretation when inflammation is marked, particularly if intraurothelial in location
Therapy-associated atypia:

- All forms of therapy:
  - Nucleomegaly with prominent nucleoli
- Topical therapy (mitomycin C):
  - Cytoplasmic vacuolization, multinucleation particularly superficial cells
- Chemotherapy (cyclophosphamide):
  - Nucleomegaly with smudged nuclear chromatin
RADIATION ATYPIA
INTRAVESICAL THERAPY
Polyoma virus

Isolated or clusters of markedly atypical cells
: ? pagetoid CIS
Polyoma Virus Infection

- Usually non-pathogenic
- May be seen in immunocompromised patients
- More frequently seen in urine cytology
- Large homogenous inclusions in enlarged cells
ALL THAT IS PAPILLARY BLADDER IS NOT PAPILLARY NEOPLASIA

The diagnosis of papillary urothelial neoplasia is made on the basis of the presence of a fibrovascular core.
Papillary tumor

Micropapillary U Ca
BEFORE YOU ASSIGN A WHO (2004)/ISUP GRADE

• Make sure it is urothelial neoplasia
  - Nephrogenic adenoma, polypoid cystitis, fibroepithelial polyp
  - Non-urothelial neoplasms
Low magnification distinction

- Thin stalk (true papillary)
  - Thin fibrovascular core
  - Only 1-2 capillaries in width

- Broad, bulbous protrusions
  - > 5 capillaries in width & abundant LP

- Broad-based stalk
- Thin stalk (true papillary)
Broad-based stalk or core

- Polypoid cystitis
- Fibroepithelial polyp
- Artifacts of sampling surface urothelium
Papillary Polypoid cystitis

Cystoscopical & microscopic mimic
Papillary Polypoid cystitis
Papillary Polypoid cystitis
FIBROEPITHELIAL POLYP
ALL THAT IS PAPILLARY BLADDER IS NOT PAPILLARY NEOPLASIA

ARTIFACTS

Avulsed urothelium
Pseudopapillary folds
TIGHTLY CLUSTERED UROTHELIUM
TIGHTLY CLUSTERED UROTHELIELUM
APPROACH

• Be very hesitant to make a diagnosis of papillary neoplasia when papillae are not classic & lining is not too atypical
• Particular caution in renal pelvic and ureteral biopsies
• Additional caution in h/o stents

CLINICO-PATHOLOGIC CORRELATION IS A MUST
U Ca. with small tubules

Nephrogenic Adenoma
NEPHROGENIC ADENOMA

Pitfalls:

• Papillary surface lesions:
  D. Dx.- urothelial papilloma

• Hobnail cells, clear cells, solid architecture:
  D.Dx. - clear cell carcinoma

• Random distribution including between muscularis mucosae muscle:
  D.Dx. - adenocarcinoma or UCa with tubules

• AMACR/racemase positivity:
  D.Dx. - adenocarcinoma of prostate
NEPHROGENIC ADENOMA – THE BIG MIMICER!

**Pattern:** Papillary, polypoid, tubular, cystic, solid

**Cell type:** Cuboidal, columnar, hobnail, signet ring

**Cytoplasm:** Scant or abundant, eosinophilic or clear

**Lumen:** Empty, colloid secretions, basophilic secretions

**Pattern:** Mucosal, lamina propria or “infiltrative”
NEPHROGENIC ADENOMA
NEPHROGENIC ADENOMA
NEPHROGENIC ADENOMA

Clues to benign diagnosis:

• Characteristic admixture of patterns
• Associated inflammation
• Stromal edema
• Lack of significant cytologic atypia
• Rare to absent mitoses
• Thickened basement membrane
• Inspissated colloid-like material
FLORID REACTIVE PROLIFERATIONS

- Dome-shaped, polypoid mucosal-based lesions
- Cystoscopic or radiographic mass lesions – may be suggestive of malignancy
- **Pitfall**: Florid proliferations with accompanying atypia
  - *Mistaken for carcinoma*
FLORID REACTIVE PROLIFERATIONS

normal mucosa  →  von Brunn’s nests  →  florid proliferation of von Brunn’s nests

- cystic change

- cystitis cystica

- columnar/cuboidal cells

- cystitis cystica glandularis

- goblet cells/Paneth’s cells

- cystitis cystica glandularis with intestinal metaplasia
POST-RADIATION PSEUDOCARCINOMATOUS PROLIFERATION

- Ulceration of mucosa ±
- Pseudoinvasive nests
- Lining cells – vacuolated nuclei and cytoplasm; reactive atypia
- Wrapping around blood vessels
- Fibrin in blood vessels
- Minimal to absent mitoses
- Inflammation, edema, vascular congestion, hemorrhage, hemosiderin
- Post-RT-induced vascular changes or stromal changes +/-
Microcystic variant

Cystitis cystica glandularis
FLORID CYSTTTIS GLANDULARIS WITH MUCIN EXTRAVASTATION
FLORID CYSTITIS GLANDULARIS WITH MUCIN EXTRAVASATION

• Significant clinical, radiographic and histologic mimic of cancer

• **Clues to benign disease:**
  • *Orderly arrangement of epithelium*
  • *Lack of cytologic atypia*
  • *Lack of in situ lesion*
  • *Lack of desmoplasia*
  • *Lack of cells floating in mucin*
MULLERIANOSIS

- Endometriosis, endocervicosis, endosalpingiosis
- Often occur together – mullerianosis
- Predominantly mural-based +/- mass formation – concern for malignancy
- Women, reproductive age group, history of cesarean section (males in hormone therapy – prostate ca)
- Size : 2-5 cms
- Hematuria, mucosuria
Pseudosarcomatous stromal reaction
PSEUDOSARCOMATOUS MYOFIBROBLASTIC PROLIFERATIONS

Synonyms:

- Pseudotumor
- Inflammatory pseudotumor
- PSFMT
- Inflammatory myofibroblastic tumor
- Inflammatory fibromyxoid (pseudo) tumor
- Pseudomalignant spindle cell proliferation
- Post-operative spindle cell tumor
PSEUDOSARCOMATOUS MYOFIBROBLASTIC PROLIFERATIONS (PMP)

- 11% multifocal
- Myxoid changes more likely to be superficial
- Fasicular/cellular areas more likely to be deep
- Nodular/fasciitis-like look
- Arborizing granulation – tissue-type vasculature
- Inflammation (acute and chronic) in stroma
- Spindle, stellate, ganglion-like cells
- Cytokeratin (93%) or muscle markers (SMA 64%, desmin 44%) not useful with differential diagnosis
PMP

Gross

- Exophytic-polypoid mass
- Soft and gelatinous
- Less commonly - white submucosal or intramural mass
- Size 1-9 cm
PSEUDOSARCOMATOUS MYOFIBROBLASTIC PROLIFERATIONS (PMP)/IMT

- In spite of muscle invasion, necrosis, cellularity, outcome uniformly favorable
- Large lesions may recur (incomplete excision or persistent reaction to resection); metastasis not documented
- Progression to sarcoma (rare)
- Alk-1 IHC (42%) and t(2:5) in situ controversial
ROLE OF IMMUNOHISTOCHEMISTRY IN THE DIAGNOSIS OF TUMORS AND TUMOR-LIKE LESIONS OF THE BLADDER: New and Exciting Markers

Mahul B. Amin
Professor & Chairman, Department of Pathology
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Los Angeles, CA
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IHC IN BLADDER PATHOLOGY

- Proving urothelial differentiation e.g. in metastatic tumor
- Flat intraepithelial lesions
- Staging of bladder cancer
- Glandular lesions
- Spindle cell lesions
<table>
<thead>
<tr>
<th>Carcinoma of unknown origin or patient with history of bladder cancer:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lymph node</td>
</tr>
<tr>
<td>• Lung</td>
</tr>
<tr>
<td>• Liver</td>
</tr>
<tr>
<td>• Bone</td>
</tr>
<tr>
<td>• Prostate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&quot;Unusual carcinoma&quot; in the bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic tumors to the bladder:</td>
</tr>
<tr>
<td>• Melanoma</td>
</tr>
<tr>
<td>• Prostate</td>
</tr>
<tr>
<td>• Colorectal</td>
</tr>
<tr>
<td>• Cervix</td>
</tr>
<tr>
<td>• Ovary</td>
</tr>
<tr>
<td>• Renal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary urothelial carcinoma:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UCa with small tubules</td>
</tr>
<tr>
<td>• Plasmacytoid</td>
</tr>
<tr>
<td>• Micropapillary</td>
</tr>
<tr>
<td>• Etc</td>
</tr>
</tbody>
</table>
CA in a cervical LN.
CA in the bladder, h.o of lung cancer
UROTHELIAL CARCINOMA
(Prim. or Metastatic site)

Challenges:
- Poorly differentiated carcinoma
- “Characterless”: solid, nested & trabecular architecture

Hallmarks:
- Frequent squamous and/or glandular diff.
- Cells with nuclear grooves
- Nuclear atypia obvious +/- anaplasia

Approach
- Clinical history (invasive, usually high stage carcinoma)
- Compare with primary
- Judicious IHC: ? Best markers
• Diagnosis of metastatic urothelial cancer
  • CK7 (+) (>90%)
  • CK20 (+) (40-70%)
  • Uroplakin III (+) (50-80%)
  • GATA3 (60-70%)
  • S100P (70-80%)
  • Thrombomodulin (+) (60-75%)
  • High molecular weight cytokeratin 34βE12 (+) (60-90%)
  • p63 (+) (60-90%)
  • CEA, Leu-M1 (±) (minimal value)
HWMCK- Invasive Tumor
Plasmacytoid
U.Ca - CK20
GATA 3 & S100P

- Markers of urothelium and urothelial carcinoma by cDNA microarray

S100P (commercial)

- Nuclear staining accompanied by cytoplasmic staining
- More sensitive but less specific than GATA3
- More specific and less sensitive than S0084
GATA3

- Nuclear staining
- lower sensitivity but higher specificity than S100P for urothelium
## GATA 3 & S100 P: Diagnostic utility

<table>
<thead>
<tr>
<th></th>
<th>Prostate carcinoma</th>
<th>Urothelial carcinoma</th>
<th>Renal cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S100P(S0084)</strong></td>
<td>3% (n=260)</td>
<td>86% (n=295)</td>
<td>1% (n=133)</td>
</tr>
<tr>
<td><strong>S100P (commercial)</strong></td>
<td>2% (n=256)</td>
<td>78% (n=300)</td>
<td>0% (n=137)</td>
</tr>
<tr>
<td><strong>GATA-3</strong></td>
<td>0% (n=308)</td>
<td>67% (n=308)</td>
<td>0%</td>
</tr>
</tbody>
</table>
PARAGANGLIOMA
PARAGANGLIOMA OF THE BLADDER – DIFFERENTIAL DIAGNOSIS

Immunohistochemistry

• Synaptophysin, chromogranin: paraganglioma
• Keratin, synaptophysin, chromogranin: carcinoid tumor
• CK7, CK20, HMWCK, p63, S100 p, GATA3: urothelial ca
• PSA, PSAP (+), p63, HMWCK (-): metastatic prostate ca
• S100A, RCC, CD10, keratin: metastatic RCC
• S-100, HMB-45, Melan-A, MiTF: metastatic melanoma
• Hepar-1: Hepatoid adenocarcinoma of the bladder
Identification of Succinate Dehydrogenase-Deficient Bladder Paragangliomas

• While the rate of SDH deficiency in paragangliomas in general is known to be approximately 30%, a significant subset (27%) of bladder paragangliomas are SDH-deficient.
• SDHB IHC may have a role in bladder paragangliomas identifying those at risk at familial predisposition and those at risk for progression.
• Identifying an SDH-deficient tumor can be prognostically significant: tumors with SDHB mutations are more likely to pursue a malignant course.

CIS

REACTIVE ATYPIA
IMMUNOHISTOCHEMISTRY IN FLAT LESIONS OF THE BLADDER

Panel:  p53, CD44 (standard isoform), CK20

Indications:
• Marked denudation – residual basal cells vs “clinging” CIS
• Distinction between reactive atypia and CIS (large cell non-pleomorphic or “small” cell)
• Pathologist favors CIS but has reservations making diagnosis
• CIS with unusual morphology – Pagetoid, undermining, etc.

Caveats:
• Not applicable for dysplasia vs CIS
• Limited experience with treated CIS
NORMAL

p53
CD-44
REACTIVE UROTHELIUM
CK-20
Regenerative basal cells vs. clinging CIS
Radiation-Reactive

Radiation CIS
2 types of muscle - awareness important for pT staging

LP inv. (M. mucosae)- pT1

M. propria inv. - pT2
AUA GUIDELINE 2007 UPDATE:

• Standard: For patients with lamina propria invasion (T1) but without MP in the specimen, repeat resection should be performed prior to additional intravesical therapy

http://www.auanet.org/guidelines/
Typical

Hypertrophic-Haphazard

Hypertrophic-\textit{M. propria-like}

\textit{M. MUCOSAE}
Typical pattern:

- Arranged in groups
- Distinct compact bundles
- Smooth outline of bundles
- Several layers both horizontally and vertically
Muscularis mucosae or muscularis propria?
Muscularis mucosae or muscularis propria?
IMMUNOHISTOCHEMICAL MARKERS IN BLADDER STAGING

- Collagen 4
- Smooth muscle actin (muscle & desmoplasia)
  - minimal value
- H-caldesmon
- Smooth muscle myosin heavy chain
  - useful for desmoplasia vs. muscle

Need for a marker to distinguish MM for MP
SMOOTHELIN
- Contractile protein
- Fully differentiated muscle cells
- Hyperplastic muscularis mucosae (-) to weak
- Diffuse and strong positivity specific for muscularis propria

Validated by Miyamoto et. al. Am J Surg Pathol. 2010
- Emphasize overlap in staining pattern and caution in interpretation
Smoothelin hyperplastic
Hypertrophic muscularis mucosae
SMA – M. Mucosae
Smoothelin – M. Mucosae
SMOOTHELIN IN DESMOPLASIA: NEGATIVE
CAUTERY: MINIMAL EFFECT ON IHC
TYPES OF MUSCULARIS PROPRIA INVASION

- In between muscle bundles
- Into muscle bundles
- Fracturing /splaying muscle bundles
M. Mucosae vs. M. Propria in TURBT

SPLAYING/FRACTURING
Splayed muscularis propria
M. Mucosae vs. M. Propria in TURBT
Smoothelin: Negative – Suggestive of M. Mucosae
Virtually any tumor from the body can spread to the bladder on occasion. Problem areas:

Enteric morphology: Colon and appendiceal primary vs. bladder primary

- Morphologically identical
- May have a surface well-differentiated “villous adenoma” surface component
- Helpful features: - Clinical history of high-stage colon cancer
  - Absence of intestinal metaplasia
- Immunohistochemistry (CK7, CK20, CDX2) not helpful (β-catenin, nuclear positivity, limited role)
METASTASIS TO THE BLADDER

Prostate vs. Urothelial Carcinoma with Glandular Differentiation vs. Primary Adenocarcinoma

- PSA
- PSAP
- PSMA
- Prostein (P501S)
- NKX1.3
- ERG-TMPRSS2
- p63
- HMWCK
- GATA3
- S100p
- Thrombomodulin

CAUTION: Both may coexist!
New Prostate Lineage Associated Markers

Protein (P501S):
- Prostatic carcinoma independent of Gleason pattern and metastatic status
- Rarely in villous adenoma and adenocarcinoma of bladder

NKX3.1:
- Prostatic epithelium, testis, bronchial mucous glands, rare ureteral urothelial cells
- Prostatic carcinoma and infiltrating lobular carcinoma

Prostate Specific Membrane Antigen (PSMA):
- Prostatic epithelium, endometrial glands, duodenal mucosa, proximal renal tubules, urothelium, neuroendocrine cells of colonic crypts and endothelium
- Prostatic adenocarcinoma, gastric carcinoma, small cell carcinoma of lung, urothelial carcinoma and GBM
Urothelial Carcinoma vs. Prostatic Carcinoma

UCa

PCa
Concurrent PCa & UCa
Urothelial carcinoma

Prostatic adenocarcinoma

ERG IHC
Clear cell Ca  Neph. adenoma
Clear cell Ca

Neph. adenoma
<table>
<thead>
<tr>
<th></th>
<th>Nephrogenic adenoma</th>
<th>Clear cell adenoCa of bladder</th>
<th>Urothelial Ca with glandular morphology</th>
<th>Prostatic adenoCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pax2/8</td>
<td>90%</td>
<td>10-20%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>AMACR</td>
<td>100%</td>
<td>75%</td>
<td>Frequently positive</td>
<td>70-100%</td>
</tr>
<tr>
<td>S100A1</td>
<td>94%</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ki67 % + nuclei</td>
<td>2-5%</td>
<td>40-50%</td>
<td>30-40%</td>
<td>2-25%</td>
</tr>
<tr>
<td>PSA</td>
<td>0 -2%</td>
<td>0</td>
<td>0</td>
<td>70-100%</td>
</tr>
</tbody>
</table>
Spindle cell lesions of bladder

- Pseudosarcomatous myofibroblastic proliferations (pseudotumor)
- Sarcomatoid carcinoma
- Leiomyosarcoma
PMP / Pseudotumors
PSFMT/ PMP

Immunohistochemistry

- Vimentin positive (don’t need it !)
- Smooth muscle actin positive
- Cytokeratin may be positive
- Desmin may be positive
  - Myofibroblastic lesion
Keratin-AE1/AE3

Desmin
Sarcomatoid urothelial carcinoma
Leiomyosarcoma
Spindle cell lesions

Benign (PMP) vs. Malignant - H&E diagnosis

- **PMP / PSFMT**
  - keratin(+/-), SMA(+), desmin(+/-), p63(-), Alk-1(+)

- **Sarc. Ca**
  - keratin (+/-), SMA(-), desmin(-), p63(+-), Alk-1 (-), HMCK & CK5/6 (+)

- **LMS**
  - keratin (-/+-), SMA(+), desmin(+), Alk1(-/+-), p63(-)
Tubulointerstitial lesions

Ian Roberts
Oxford, UK
Renal Pathology for the general pathologist:
Recognising lesions in tumour nephrectomy specimens
The kidney at autopsy – renal lesions that kill
A flavour of medical renal disease
Normal and atrophic tubules
Tubulointerstitial inflammation
Things in tubules
Acute tubular injury
Tubules - Normal
Tubules - Normal
Tubules - Atrophy

Distribution gives an indication of cause:

Multifocal: Chronic glomerular/small vessel disease

Diffuse: Tubulointerstitial disease

Segmental: Reflux nephropathy/chronic obstructive pyelonephritis

Peritumoral: Local obstruction
Interstitial inflammation - tubulointerstitial nephritis

**Terminology issues:**

Beware acute and chronic – these are clinical, not histological, terms in the kidney.

Use “active” for an active inflammatory process and give a measure of fibrosis as an indication of chronicity.

Never use the term “chronic inflammation”

Mononuclear inflammatory cell infiltrates are a non-specific feature of fibrosis whatever the aetiology.

Tubulointerstitial nephritis has a specific meaning for autoimmune attack on the tubules, usually triggering steroid treatment.
Interstitial inflammation - tubulointerstitial nephritis
Tubulointerstitial nephritis

Classification by cause:

Drug-associated

  PPIs, antibiotics, NSAIDS + many others

Associated with systemic autoimmune disease

  SLE, Sjogrens, TINU

Infections

  bacterial, viral

Sarcoidosis

Localised inflammation around tumours in nephrectomy specimens is not tubulointerstitial nephritis.
Tubulointerstitial nephritis

The nature of the infiltrate differs according to cause – but not specific.

Clinical history is essential
CKD, previous tuberculosis, HCV positive, granulomatous hepatitis 1 year ago

Diagnosis?
AKI, ANCA positive, cortex – TIN, glomeruli normal

Diagnosis?
AKI, ANCA positive, cortex – TIN, glomeruli normal

Diagnosis?
Beware TIN + red cell casts
In renal biopsies cut through the block looking for vasculitic lesions if not present in initial sections
Red cell casts in tumour nephrectomy specimens – look for glomerular lesions, consider other causes – previous needle biopsy, embolisation
Male 59 years. Acute rise in creatinine 80-215 in 2 months.
Low complement and hypergammaglobulinaemia. Two month history of
weight loss and poor appetite. Mass in head of pancreas and increased LFTs.
Large ?infiltrated kidneys on CT.

Diagnosis?
Male 59 years. Acute rise in creatinine 80-215 in 2 months. Low complement and hypergammaglobulinaemia. Two month history of weight loss and poor appetite. Mass in head of pancreas and increased LFTs. Large ?infiltrated kidneys on CT.

Diagnosis?
35 patients with IgG4-TIN:
- 27 (77%) had acute or progressive chronic renal failure
- 29 (83%) had involvement of other organ systems
- 18 of 23 (78%) had radiographic abnormalities.
- Elevated total IgG or IgG4 serum levels in 79%.

All showed a plasma cell–rich TIN, with most showing diffuse interstitial fibrosis. Immune complexes along the tubular basement membranes were present in 83%. All specimens had an increase in IgG4 plasma cells by immunohistochemistry. Using a control group of 175 specimens with plasma cell–rich interstitial infiltrates, IgG4 immunohistochemistry had a sensitivity of 100% and a specificity of 92% for IgG4-TIN. (TIN associated with pauci-immune TIN also frequently shows increased numbers of IgG4 positive plasma cells.) Of the 19 patients with renal failure for whom treatment and follow-up data were available, 17 (89%) responded to prednisone.
## IgG4-related TIN

### Table 3. Proposed diagnostic criteria for IgG4-related TIN

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Plasma cell–rich tubulointerstitial nephritis with &gt;10 IgG4 + plasma cells/hpf field in the most concentrated field&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement</td>
</tr>
<tr>
<td></td>
<td>Diffuse marked enlargement of kidneys</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>Elevated serum IgG4 or total IgG level</td>
</tr>
<tr>
<td><strong>Other organ involvement</strong></td>
<td>Includes autoimmune panceatitidis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis</td>
</tr>
</tbody>
</table>

Diagnosis of IgG4-TIN requires the histologic feature of plasma cell–rich TIN with increased IgG4 + plasma cells and at least one other feature from the categories of “imaging”, “serology”, or “other organ involvement”.

<sup>a</sup>Mandatory criterion.

<sup>b</sup>Supportive criterion, present in >80% of cases.

Diagnosis?

Male 70 years AKI
Male 70 years AKI

Rigors, breathless, myocarditis, 2 weeks after fishing holiday in Norfolk

Diagnosis?
Hantavirus nephropathy

Hantavirus Nephropathy

Dušan Ferluga and Alenka Vizjak

Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

ABSTRACT
Pathogenic rodent-borne hantaviruses cause in humans generalized infections that involve the peripheral vascular bed and severely affect their permeability. We describe a 30-yr-old male patient with clinical symptoms characterizing five conventional phases of hemorrhagic fever with renal syndrome after an uncommonly severe hantavirus infection with the Puumala strain. Renal biopsy in this situation typically demonstrates acute hemorrhagic interstitial nephritis, particularly pronounced in the outer medulla. Hantaviruses are not cytopathic for most cells, and their interactions with endothelial cells that activate immune mechanisms play a key role in the pathogenesis of vascular dysfunction characterizing this disease.


Diagnosis?

Diagnosis?
Infective nephritis

Ascending infection (pyelonephritis)
Haematogenous spread
Infective nephritis

Ascending infection (pyelonephritis)
Haematogenous spread
Infective nephritis

Ascending infection (pyelonephritis)
Haematogenous spread
Tubulointerstitial infiltrates in transplant kidneys:
T-cell mediated rejection
Viral nephritis
TIN?

Diagnosis?
PVN can be seen in native kidneys

Less common than in renal transplants but multiple case reports of PVN in the native kidneys of recipients of heart, lung and pancreas transplants.

57 year-old man developed renal failure due to BKV nephropathy one year after starting chemotherapy for CLL.


Native kidney polyoma virus nephropathy, urothelial ulceration, and renal pelvic fibrosis presenting as a mass lesion in a non-debilitated, apparently immunocompetent man. Go S et al. Int Urol Nephrol 2011
Tubulointerstitial infiltrates in transplant biopsies:
T-cell mediated rejection
Viral nephritis
TIN?

Diagnosis?
Tubulointerstitial infiltrates in transplant biopsies:
T-cell mediated rejection
Viral nephritis
TIN?

Diagnosis?
Oxalate - commonest tubular crystallopathy

1. Inherited enzyme deficiencies in the metabolism of glyoxylate and its precursors (primary hyperoxaluria types I and II).
2. Vitamin B6 deficiency that results in increased conversion of glyoxylate to oxalate rather than glycine.
3. Increased ingestion of oxalate precursors such as ethylene glycol and ascorbic acid.
4. Increased absorption of oxalate in the gut (enteric hyperoxaluria).

Clinical history is important

Diagnosis?
Acute phosphate nephropathy

First case reported by Desmeules et al. *N Engl J Med* 2003;349:1006

21 patients presenting with acute renal failure, were normocalcemic, and had a history of recent colonoscopy preceded by bowel cleansing with oral sodium phosphate solution. All developed chronic renal insufficiency, 4 requiring haemodialysis.

![Acute phosphate nephropathy](image-url)
Diagnosis?
Diagnosis?
Diagnosis?
Acute tubular injury

Ischaemia, drugs & toxins, filtered proteins

Clinical history is important

Mechanisms of tubular injury associated with drugs:

Direct tubular epithelial injury

Tubulointerstitial nephritis

Ischaemic tubular injury associated with vasospasm/vascular injury

Indirect injury associated with haemolysis/rhabdomyolysis

Metabolic disturbances, eg Orlistat

Some drugs, eg. NSAIDs. may cause injury through multiple mechanisms
Light chain tubulopathy

Typically associated with kappa light chains

Varied clinical presentation:

Proteinuria
Acute kidney injury
Tubular dysfunction/acquired Fanconi syndrome
Light chain tubulopathy
Light chain tubulopathy

kappa

lambda
Acute tubular injury in the post mortem kidney

Features of mild acute tubular necrosis (dilated tubules, flattened epithelium, regenerative changes) are obscured by autolysis.

Renal biopsy

Post-mortem kidney
Acute tubular injury in the post mortem kidney

Post-mortem autolysis resembles severe acute tubular necrosis - inflammation is absent in both.
Acute tubular injury in the post mortem kidney

Necrotic cells in the lumen of a tubule with an intact epithelium indicates flow in the tubule following cell death.
Acute tubular injury in the post-mortem kidney

Necrotic cells in the lumen of a tubule with an intact epithelium indicates flow in the tubule following cell death.

Renal biopsy

Post-mortem kidney
Drug-associated tubular injury

Drugs that cause direct tubular epithelial injury:

- Antibiotics
- Immunosuppressive drugs (CNI, sirolimus)
- Antiviral agents
- Chemotherapeutic agents (cisplatin, methotrexate, others)
- Herbal medications (aristolochic acid)
- Radiological contrast media
- Anaesthetic agents
Tacrolimus toxicity

Diagnosis?
Gentamicin toxicity

Diagnosis?
Drug-associated tubular injury

Mechanisms of epithelial injury and morphology are varied:

Antiretroviral agents – Tenofovir

Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities

Leal C. Herlitz¹, Sumit Mohan³, Michael B. Stokes¹, Jai Radhakrishnan², Vivette D. D’Agati¹ and Glen S. Markowitz²
Drug-associated tubular injury

Mechanisms of epithelial injury and morphology are varied:
Aristolochic acid (Chinese herbs nephropathy; Balkan nephropathy)
Glomerular lesions

Ian Roberts
Oxford, UK
Renal Pathology for the general pathologist:
Recognising lesions in tumour nephrectomy specimens
The kidney at autopsy – renal lesions that kill
A flavour of medical renal disease

Normal glomeruli
Sclerosis
Proliferation and necrosis
Tumour nephrectomy specimens

Things to remember:

Urologists have little or no interest in nephrology
They may be unaware that their patient has a medical disease that may affect the kidney
If they are aware, they wouldn’t dream of informing the pathologist
Typical clinical details: “Left kidney – tumour”
If you see an abnormality, check the patient’s biochemistry
Don’t wait for a call from the nephrologist 3 months later – “this patient has CKD – what’s the diagnosis?”
Tumour nephrectomy specimens

Commonest lesions in renal parenchyma:

Infective/obstructive changes secondary to the tumour
Chronic vascular disease
Hyperfiltration changes – glomerulomegaly and secondary FSGS
Diabetic nephropathy
IgA nephropathy
Other GNs
Glomeruli - Normal
Glomerular lesions - sclerosis

Sclerosis - segmental  global  nodular
Nodular glomerulosclerosis

Diabetic glomerulopathy
Idiopathic nodular glomerulosclerosis
Amyloidosis (not sclerosis)
Light chain deposition disease/MIDD
Immunotactoid glomerulopathy
Fibrillary GN
Diabetic nephropathy

Earliest change at LM is glomerulomegaly

\[\downarrow\]

Diffuse mesangial sclerosis

\[\downarrow\]

Nodular glomerulosclerosis

Other manifestations of diabetic vascular disease:

Arteriolar hyalinosis

Atheroemboli
Diabetic nephropathy: thickened basement membrane on EM
Diabetic nephropathy: Linear GBM positivity for IgG
Diabetic nephropathy: Diffuse mesangial sclerosis
Diabetic nephropathy: Nodular sclerosis
Diabetic nephropathy: Insudative lesions
Amyloidosis
Amyloidosis

Congo red
Amyloidosis
Amyloidosis
Amyloidosis

Beware!
Congo red may be negative:
Thin section
Very little amyloid
Poor stain

False positive Congo red: look for anomalous colours under polarised light
Immunotactoid  Fibrillary GN
Immunotactoid  Fibrillary GN

0.06% of renal biopsies  0.6% of renal biopsies
IgG dominant in 83%  IgG dominant & polyclonal in 96%
Monoclonal in 67%

Presentation is similar for the two – renal failure, proteinuria (50% nephrotic), haematuria.

Histology is variable – various combinations of mesangial & endocapillary proliferation, membranoproliferative change, segmental & global sclerosis.

Light chain deposition disease
Light chain deposition disease
Light chain deposition disease
Focal segmental glomerulosclerosis

- is a lesion – focal segmental sclerosis (actually multiple lesions that are often diffuse and may not show sclerosis…)
- is a clinicopathological entity, in which nephrotic syndrome is associated with focal segmental glomerular lesions
- the aetiologies are diverse and multiple
- the morphology to some extent reflects the aetiology and predicts prognosis
Idiopathic

Known cause of podocyte injury
1. Genetic: eg. podocin, nephrin, WT-1, mutations
2. Infective: eg. HIV, parvovirus B19, CMV
3. Drug-induced: eg. Pamidronate, lithium, IFN-α

FSGS

Glomerular hypertension/hyperfiltration
1. Reduced nephron mass: eg reflux nephropathy, nephrectomy, renal dysplasia, unilateral renal agenesis
2. Increased stress on normal nephron numbers: obesity, hypertension, sickle cell anaemia

Non-specific scars following inflammatory injury
eg. Vasculitic GN, IgAN/HSP nephritis, Lupus
Focal segmental glomerulosclerosis
Perihilar variant

- Sclerosis and hyalinosis adjacent to the vascular pole.
- Associated with secondary (hyperfiltration) FSGS, eg obesity, hypertension.
- Non-sclerosed glomeruli are frequently enlarged (glomerulomegaly).
Focal segmental glomerulosclerosis

Podocytopathy

- Podocyte hypertrophy and hyperplasia
- Protein resorption droplets in podocytes
- Loss of foot processes on EM
- Nephrotic proteinuria
Focal segmental glomerulosclerosis
Collapsing variant
Glomerular tip lesion

A manifestation of heavy proteinuria.

May be seen in association with minimal change disease, FSGS, membranous, diabetes, post-infectious GN, etc.

If it is the only glomerular abnormality, response to steroid treatment and prognosis is similar to minimal change disease.
Mesangial hypercellularity = 4 or more mesangial cell nuclei per peripheral segment (in 3 micron thick section).

Commonest cause of mesangial hypercellularity in a nephrectomy specimen is a thick section.

If in doubt ask for a 3 micron section stained with PAS.
Glomerular lesions: proliferation

Mesangial hypercellularity = 4 or more mesangial cell nuclei per peripheral segment (in 3 micron thick section).

Commonest cause of mesangial hypercellularity in a nephrectomy specimen is a thick section.

If in doubt ask for a 3 micron section stained with PAS.

Mesangial hypercellularity (proliferation)
Glomerular lesions: proliferation

Extracapillary (crescent)  Endocapillary
IgA nephropathy

Commonest glomerulonephritis

Variable clinical presentation (microscopic haematuria, nephrotic proteinuria, acute renal failure)

Variable histology (normal by light microscopy to crescentic GN)

Diagnosis based on the presence of IgA-predominant immune deposits in glomeruli - usually mesangial
The diagnosis of IgA nephropathy is based on immunohistology
Mesangial deposits have a characteristic location.
The histology of IgA nephropathy is heterogeneous.
Classification of IgA nephropathy

Oxford Classification

Minimum prognostic data:

Glomerular “pattern”:
Mesangial hypercellularity in > or <50% of glomeruli  
(M 0/1)
Endocapillary hypercellularity – present/absent  
(E 0/1)
Segmental sclerosis/adhesions – present/absent  
(S 0/1)
Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, >50%  
(T 0/1/2)

In addition:  Total number of glomeruli
   Endocapillary proliferation - %
   Cellular/fibrocellular crescents - %
   Necrosis - %
   Global glomerulosclerosis - %

Example summary line: There is an IgA nephropathy showing diffuse mesangial proliferation with focal segmental sclerosis and moderate chronic tubulointerstitial damage (M1,E0,S1,T1)
Mesangiocapillary GN
= Membranoproliferative GN

MPGN is a morphology, not a diagnosis - mesangial cell proliferation (producing accentuated lobularity) + duplication of the GBM

Lupus nephritis
IgA nephropathy
Cryoglobulinaemic GN
Chronic post-infectious GN
MIDD
C3 glomerulopathy
Idiopathic immune complex GN
MPGN, type I

- Haematuria, proteinuria, nephrotic syndrome, renal failure
- $\text{C3} \pm \text{IgG}$ in capillary walls
- Subendothelial deposits at EM & mesangial cell interposition

C3 glomerulopathy
Idiopathic immune complex-mediated GN
Mesangiocapillary GN, type I
C3 glomerulopathy

= Isolated C3 deposits in glomeruli
Reflects over-activation of the alternative complement pathway – due to autoantibodies (eg. C3NeF/anti-C3bBb), inherited mutations/deficiency of complement regulatory proteins.

- DDD
- C3GN
- CFHR5 nephropathy

(A dog’s dinner of a classification – a mix of pathogenesis and morphology. Multiple pathogenetic factors can result in one morphology – eg. DDD – mutations of CFH, CFI, C3, autoAbs - C3NeF, anti-CFB, anti-CFH, etc)
MPGN and C3 glomerulopathy are both morphological labels. DDD used to be called MPGN type II – but only a minority of DDD show an MPGN pattern.

Not all C3 glomerulopathy is MPGN pattern and not all MPGN pattern is C3 glomerulopathy.
Dense deposit disease

Haematuria (90%), nephrotic syndrome (50%), acute nephritic syndrome (20%)
Variable LM - mesangial cell proliferation, MPGN, focal endocapillary proliferative, eosinophilic thickening of capillary walls
C3 in capillary walls
Replacement of basement membrane by linear masses of electron dense material
Dense deposit disease
Dense deposit disease
Glomerular lesions: necrosis

Rupture of basement membranes, fibrin exudation, karyorrhexis
Crescentic glomerulonephritis

**Vasculitic**
- Pattern of disease: focal segmental, necrosis-sclerosis
- IH: pauci-immune
- Other GNs: as for non-crescentic forms

**Anti-GBM disease**
- Pattern of disease: diffuse global, synchronous
- IH: linear IgG & C3
Renal vasculitis

May be isolated renal vasculitis or associated with systemic vasculitis. Common association with pulmonary haemorrhage (Goodpasture’s syndrome).

80% are ANCA-positive

c-ANCA (anti-PR3): lesions are of similar age
p-ANCA (anti-MPO): lesions typically at various stages from acute necrotising to fibrotic

Histology of ANCA-negative cases is the same as the ANCA-positive
Renal vasculitis

Arteritis (approx. 20%)
Renal vasculitis

European vasculitis study group:
Best histological predictors of long term renal function:
% normal glomeruli, glomerulosclerosis, interstitial fibrosis, tubular atrophy.
Best predictors of improvement of renal function from 0-18 months:
% crescents, necrosis, interstitial inflammation.

Autoantibodies to the Goodpasture antigen on the alpha 3 chain of type IV collagen

- Rapidly progressive GN +/- pulmonary haemorrhage
- Glomerular lesions typically diffuse, global & synchronous.
Autoantibodies to the Goodpasture antigen on the alpha 3 chain of type IV collagen
Rapidly progressive GN +/- pulmonary haemorrhage
Glomerular lesions typically diffuse, global & synchronous.

Anti-GBM disease
Anti-GBM disease

Linear IgG in glomerular basement membranes.
Up to 32% of patients with anti-GBM antibodies also have positive ANCA (usually anti-MPO)
Remember: multiple pathologies are common in renal disease

Male 46 years. Suffered from diabetes mellitus and chronic pancreatitis, receiving dialysis. Previous bilateral BKA. Widespread calcification of vessels within arms & legs. Died suddenly at home
Male 46 years. Suffered from diabetes mellitus and chronic pancreatitis, receiving dialysis. Previous bilateral BKA. Widespread calcification of vessels within arms & legs. Died suddenly at home.
Male 46 years. Suffered from diabetes mellitus and chronic pancreatitis, receiving dialysis. Previous bilateral BKA. Widespread calcification of vessels within arms & legs. Died suddenly at home
Male 46 years. Suffered from diabetes mellitus and chronic pancreatitis, receiving dialysis. Previous bilateral BKA. Widespread calcification of vessels within arms & legs. Died suddenly at home
Diagnoses:

Diabetic nephropathy

Oxalate nephropathy

Granulomatous tubulointerstitial nephritis secondary to sarcoidosis.
The End
Interactive Kidney Quiz

Ian S. Roberts, Oxford
Michael J. Mihatsch, Basel
Helmut Hopfer, Basel
What to do?

• Download Kidney Quiz PDF (http://pathologie.unispital-basel.ch → Aktuelles → Basel Seminars) or look at screen
• Team up with the person sitting next to you
• To vote, go to movo.ch, enter token, press submit

Token: PA JY JY MA
Test vote

How did you learn about the Basel Seminars?

1. I saw it in the newspaper
2. Email by the European Society of Pathology
3. Email by the German Society of Pathology
4. Mailing by the Swiss Society of Pathology
5. Website of the Institute for Pathology in Basel
6. I heard it from colleagues
What to do?

• Participants will study 6 macroscopic pictures and discuss their thoughts and diagnoses with another person in the audience.
• Pictures will be displayed on the main screen for 50 seconds each. The composite is shown on the voting screen
• MC-Question are shown afterwards
• Time frame 5 minutes
Set 1
What is your main diagnosis?

1. chronic glomerulonephritis
2. arteriolosclerosis
3. vascular scars
4. pyelonephritic scars
What is your main diagnosis?

1. chronic GN
2. renal infarction
3. crescentic GN
4. malignant nephrosclerosis
5. acute tubular necrosis / shock kidney
What is your main diagnosis?

1. arteriolosclerosis
2. diabetic kidney
3. acute tubular necrosis / shock kidney
4. chronic GN
5. malignant nephrosclerosis

220 g
What is your main diagnosis?

1. amyloidosis
2. acute tubular necrosis / shock kidney
3. no significant pathology
4. acute GN
What is your main diagnosis?

1. malignant nephrosclerosis
2. pyelonephritis
3. vascular scars
4. chronic GN
5. acute tubular necrosis / shock kidney
What is your main diagnosis?

1. no significant pathology
2. acute tubular necrosis / shock kidney
3. amyloidosis
4. acute GN
Solutions (I.S. Roberts)
Dg: arteriolosclerosis, vascular scars
Dg: crescentic glomerulonephritis
Dg: diabetic kidney
PathoPic

Dg: no significant pathology
Dg: malignant nephrosclerosis
Dg: amyloidosis
RCPath “Minimum” dataset for tumour nephrectomy specimens:

Size of specimen (3 dimensions)  Useless information
Weight of specimen  Useless information
Size of kidney (3 dimensions)  Unnecessary
Surface of kidney  Encourages poor dissection

Note of scarring – distribution

Cortical thickness:
>7-10mm  Normal
5-7mm  Mild atrophy
3-5mm  Moderate atrophy
<3mm  Severe atrophy

Good correlation between cortical atrophy and renal function in CKD (exceptions: diabetes, amyloidosis)
Patterns of scarring

Granular subcapsular scarring

Histology: Focal global glomerulosclerosis
Patterns of scarring

Granular subcapsular scarring:

Histology:  Focal global glomerulosclerosis
           Arteriolar hyalinosis (arteriolosclerosis)
Patterns of scarring

Granular subcapsular scarring:
Histology:  Focal global glomerulosclerosis
          Arteriolar hyalinosis (arteriolorosclerosis)
          Arterial fibroelastosis (arteriosclerosis)
Patterns of scarring

Granular subcapsular scarring:

Histology:  Focal global glomerulosclerosis
            Arteriolar hyalinosis (arteriolosclerosis)
            Arterial fibroelastosis (arteriosclerosis)

Causes:    Age-related nephrosclerosis
            Essential hypertension
            Diabetic microangiopathy
Patterns of scarring

Deep pitted cortical scars:
Patterns of scarring

Deep pitted cortical scars:
Patterns of scarring

Deep pitted cortical scars:

Histology:  Segmental global glomerulosclerosis
            Segmental interstitial fibrosis and tubular atrophy
            Arterial fibroelastosis ± atheroemboli
Patterns of scarring

Deep pitted cortical scars:

Histology: Segmental global glomerulosclerosis
           Segmental interstitial fibrosis and tubular atrophy
           Arterial fibroelastosis ± atheroemboli

Causes: Macrovascular disease with athero/thromboemboli
Patterns of scarring

Segmental transcortical scars with distortion of collecting system:
Causes: Obstruction/reflux ± infection
Patterns of scarring

Segmental transcortical scars with distortion of collecting system:

Histology: Glomerulosclerosis and interstitial fibrosis
          Dilated atrophic distal tubules containing uromodulin casts ("thyroidisation")
          Arterial fibroelastosis
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)
Endothelial injury
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)

Endothelial injury
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)
Endothelial injury
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)

Endothelial injury → proliferative response
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)

Endothelial injury → proliferative response → intimal fibrosis
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)
Endothelial injury $\rightarrow$ proliferative response $\rightarrow$ intimal fibrosis
Malignant hypertension

A cause of arterial thrombotic microangiopathy (malignant vascular disease)

Ischaemic injury
Malignant vs benign vascular disease
Set 2
What is your main diagnosis?

1. gout nephropathy
2. septikopyemia
3. granulomatous interstitial nephritis
4. ascending pyelonephritis
What is your main diagnosis?

1. collecting duct carcinoma
2. leukemia/lymphoma
3. megalocytic interstitial nephritis
4. malakoplakia
5. xanthogranulomatous pyelonephritis
What is your main diagnosis?

1. metastasis
2. septikopyemia
3. ascending pyelonephritis
What is your main diagnosis?

1. necrotizing papillitis
2. hydrenephrosis
3. urolithiasis
4. chronic GN
5. Randall plaques
What is your main diagnosis?

1. renal tuberculosis
2. hydronephrosis
3. collecting duct carcinoma
4. urothelial carcinoma
5. xanthogranulomatous pyelonephritis
What is your main diagnosis?

1. Randall plaques
2. papillary necrosis
3. renomedullar interstitial tumor
4. papillary nephrocalcinosis
5. gout nephropathy
6. amyloidosis
Solutions (M.J. Mihatsch)
Description

Involvement of cortex and medulla
Yellowish foci and stripes
Surrounded by hyperemia or hemorrhage
Unaffected pelvic mucosa

Diagnosis:
Septicopyemic foci

Differential diagnosis:
Pyelonephritis
Note no involvement of pelvic mucosa!

However in some cases it may be impossible to differentiate between both.
Description
Involvement of cortex and medulla
Yellowish stripes and foci, partially confluent
Massive hyperemia and/or hemorrhage
Hyperemia of pelvic mucosa

Diagnosis
Acute pyelonephritis

Differential diagnosis
I have difficulties to think of anything else
Description
enlargement of the kidney:
(legth: 14 cm)
Extensive hemorrhagic necrosis of medulla and cortex
Surrounded by broad yellow rim
Hydronephrosis
Necrosis and hyperemia of pelvic and ureteral mucosa

Diagnosis
Xantho (granulo) matous
Pyelonephritis

Stone removed
(was in place of the ulcer in the ureter)

Differential diagnosis
Stone-Pyonephrosis (75%)(C:10%)
Tuberculosis (15%) (C: 5%)
Tumor (10%) (C:10%)
Correct (adults 0%, children 25%)
Clear cell carcinoma

Keep in mind: granulomas may be absent (Xanthommatous p.)
Description
Whitish discoloration and stripes limited to the medulla
Stripes start at the papillary tip
No other abnormalities!

Diagnosis
Papillary nephrocalcinosis or Randall plaques or Kalk „Infarkt“

Differential diagnosis
Acute uric acid nephropathy
Papillary fibrosis
Papillary amyloidosis
Differential diagnosis

Acute uric acid nephropathy

Pap. amyloidosis
Description
Massive enlargement of the kidney
(length: 17 cm)
Involvement of the whole kidney
Whitish nodules throughout the cortex
more than medulla
No abnormalities in other compartments
Note: no necrosis!

Diagnosis
Malacoplakia or megalocytic interstitial nephritis

Differential diagnosis
Malacoplakia or megalocytic interstitial nephritis
Neoplasia especially:
Malignant lymphoma or other
Differences between megalocytic IN and malacoplakia:

Michaelis Gutmann bodies and nothing else

Michaelis Gutmann bodies are PAS and Kossa positive
Description
Brownish discoloration of papilla
Deformation of papilla
Dilatation and hyperemia of pelvic mucosa

Yellowish discoloration of parenchyma
Granularity of the surface

Diagnosis
Papillary necrosis
<Necrotizing papillitis in diabetes>

Differential diagnosis
Phenacetin kidney
Differential diagnosis of papillary necrosis see below
Comments to papillary necrosis
Papillary necrosis

Pg: i.e. vascular problem

The capillaries supplying the papilla are up to three cm long. The blood (oxygen) supply of the medulla is poor.
## Prevalence of Lesions of the Renal Papilla
### (in 616 Patients / 1220 Kidneys)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Both sides n (% of kidneys)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients /kidneys (n)</td>
<td>616 / 1220</td>
</tr>
<tr>
<td>No significant lesions of the papilla</td>
<td>1045 (85.7)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>90 (7.4)</td>
</tr>
<tr>
<td>Focal fibrosis</td>
<td>87 (7.1)</td>
</tr>
<tr>
<td>Complete fibrosis</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>102 (8.4)</td>
</tr>
<tr>
<td>Areactive necrosis of the papillary tip</td>
<td>56 (4.6)</td>
</tr>
<tr>
<td>Areactive focal necrosis</td>
<td>22 (1.8)</td>
</tr>
<tr>
<td>Areactive complete Necrosis</td>
<td>11 (0.9)</td>
</tr>
<tr>
<td>Necrosis in pyelonephritis</td>
<td>13 (1.1)</td>
</tr>
<tr>
<td>Others</td>
<td>46 (3.8)</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>39 (3.2)</td>
</tr>
<tr>
<td>Cystoid dilatation</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Amyloidosis of the papilla only</td>
<td>4 (0.3)</td>
</tr>
</tbody>
</table>
Papillary necrosis

**Pg**: i.e. vascular problem

The capillaries supplying the papilla are up to three cm long.
The blood (oxygen) supply of the medulla is poor.

**Remember a hosepipe:**
In case no water comes out of the hosepipe
There are several possible causes:
- No input,
- Vascular lumen obstructed,
- Vessel wall thickening and narrowing of the lumen
- Pressure from outside
Pathogenetic types of papillary necrosis

Inflammatory
- Pyelonephritis

Angiopathic
- Diabetes (w. in.)
- Nephrosclerosis,
- Amyloidosis, Vasculitis
- Renal vein thrombosis
- Shock, dehydration
- Sickle cell disease, Tx- rejection
- Phenacetin (white (rare) or black)

Compressive
- Urinary tract obstruction without infection (w.i.) (white)
Types of papillary necrosis: Extend and severity (I)
Types of papillary necrosis: Extend and severity (II)
Black papillary necrosis

Think of phenacetin
Phenacetin kidney

Keep in mind: black papillary necrosis
Phenacetin kidney

Compete necrosis of papilla and medulla
Early shedding of the necrotic papilla at the tip
Cellular infiltrates covering the necrosis
Note bone formation in the necrotic papilla which remained in situ.
Phenacetin kidney

Note massive basement hickening of peritubular capillaries
Capillary sclerosis as seen in the kidney and the urinary tract in phenacetin kidney

Early stage of capillary sclerosis with multilayering of the BM. Activated endothelium
Phenacetin kidney

Note: Massive lipid deposition in basement membranes
Yellow papillary necrosis

Think of pyelonephritis
Typical examples of papillary necrosis in pyelonephritis
Histological examples of papillary necrosis in pyelonephritis

Massive PMN

Few PMN
White papillary necrosis

Think of vascular diseases
Typical examples of papillary necrosis in vascular diseases

Think also of: Diabetes (w. in.) Nephrosclerosis, Amyloidosis
Red papillary necrosis

Think of vascular diseases
Typical examples of papillary necrosis with haemorrhage

Haemorrhage may be primary e.g. renal vein thrombosis, shock, dehydration, sickle cell disease, rejection or secondary e.g. in pyelonephritis

Hemorrhagic papillary necrosis in vascular rejection
I hope you will never overlook papillary necrosis again

Thank you for your attention
Common Challenges in Kidney Cancer

Holger Moch
Department Pathology
University Hospital Zurich
## Challenges for Pathologists

<table>
<thead>
<tr>
<th>Renal Mass Biopsies</th>
<th>Diagnostic Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Stratification</td>
<td>Prognostic Marker</td>
</tr>
<tr>
<td>Novel Treatments in Oncology</td>
<td>Predictive Marker</td>
</tr>
</tbody>
</table>
ISUP Consensus Conference

Vancouver (USCAP)
Working Group IV
(Biomarker: Diagnosis, Prognosis, Prediction)

**Group Chair** Holger Moch, **Co-chair** Liang Cheng,

**Rapporteur** Steven Shen,

**Members:** Victor Reuter, Nathalie Leclerq-Roux, Maria Merino, George Netto, Puay Hoon Tan
Do the morphotypes of RCC have prognostic significance per se:

1. Yes
2. No
Renal Tumor Biopsies for Evaluation of Small Renal Tumors: Why, in Whom, and How?

Mesut Remzi, Michael Marberger
Department of Urology, Medical University of Vienna, Vienna, Austria

Renal mass sampling: An enlightened perspective
Mary K Samplaski, Ming Zhou, Brian R Lane, Brian Herts, and Steve C Campbell
Glückman Urological and Kidney Institute, Pathology and Laboratory Medicine Institute, and Imaging Institute, Cleveland Clinic, Cleveland, Ohio, and Division of Urology, Spectrum Health Hospital System, Grand Rapids, Michigan, USA

Renal Mass Biopsy—A Renaissance?
Brian R. Lane, Mary K. Samplaski, Brian R. Herts, Ming Zhou, Andrew C. Novick, and Steven C. Campbell
From the Glückman Urological Institute (BRL, MKS, ACN, SCC) and Departments of Radiology (BRL) and Anatomic Pathology (MK), Cleveland Clinic, Cleveland, Ohio
Biopsies (66)

Adequate (52)

Benign (16)
- Oncocytoma (10)
- Angiomyolipoma (3)
- Inflammatory (2)
- Others (1)

Malignant (35)
- RCC (34)

Indeterminate; Advise excision (1)
- Clear (27)
- Papillary (6)
- Chromophobe (1)

Inadequate (14) → Advise rebiopsy
Potential of Needle Biopsy

- Diagnostic accuracy increases
  - Before 2001: 82%
  - 2001-2006: 90%
  - 2010: >95%
- Non-informative biopsies: 10-20%
- „oncocytic neoplasm“: diagnostic dilemma?
- Metastases of RCC !!
- Grading?
Can we confidently diagnose renal oncocytoma (RO) on core needle biopsy?

1. No, it is not possible to diagnose RO on core needle biopsy.
2. Yes, in the majority of the cases we can make diagnosis of RO.
3. Yes, it is always possible to diagnose RO.
4. Uncertain, not enough experience
Novel renal tumor types with clear cytoplasm

- Translocation carcinoma

- Renal Cancer in End Stage Renal Disease
  - ACD-related RCC
  - Clear cell and papillary RCC in ESRD

- Sporadic clear cell and papillary and cystic (!) renal cancer

- Leiomyomatous renal cancer

- Multilocular cystic renal cell carcinoma

- Angiomyolipoma / Epitheloid Angiomyolipoma
„Translocation“ Type of Renal Cancer in Children

no VHL-Mutations!
Morphologic and Molecular Characterization of Renal Cell Carcinoma in Children and Young Adults

Elisabeth Bruder, * Oliver Passera, * Dieter Harms, † Ivo Leuschner, † Marc Ladanyi, ‡ Pedram Argani, § John N. Eble, ¶ Kirsten Struckmann, * Peter Schraml, * and Holger Moch *

41 Carcinoma < 20 years

- clear cell 6 (15%)
- papillary 9 (22%)
- chromophobe 2
- collecting duct 2
- after neuroblastoma 1
- Translocation carcinoma 8 (20%)
- Unclassified 13 (24%)
Xp11 Translocation Carcinoma in Adults

- 14/28 pts: Stage 4
- 11/13 pts: pN1
- 5/6 pts developed hematogenous metastases

- Xp11 Translocation Carcinoma in Adults are Aggressive Cancers

Spectrum of Epithelial Neoplasms in End-Stage Renal Disease
An Experience From 66 Tumor-Bearing Kidneys With Emphasis on Histologic Patterns Distinct From Those in Sporadic Adult Renal Neoplasia

Satish K. Tickoo, MD,* Mariza N. dePeralta-Venturina, MD,†‡ Lara R. Harik, MD,* Heath D. Worcester, MD,§ Mohamed E. Salama, MD,† Andrew N. Young, MD,§ Holger Moch, MD,‖ and Mahul B. Amin, MD§
Should Acquired Cystic Disease-RCC be Recognized as an Entity at this time?

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Clear cell-papillary RCC, sporadic (!)
Clear cell papillary RCC has:

1. POOR OUTCOME
2. GOOD OUTCOME
Should CCPRCC/CCTPRCC be Recognized as an Entity at this time?

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Which name should be used for this tumor?

1. Clear cell papillary renal cell carcinoma (CCPRCC)
2. Clear cell tubulopapillary renal cell carcinoma (CCTPRCC)
3. Other
Do you think CCPRCC/CCTPRCC and RAT are related?

1. They are probably the same entity
2. They are probably different entities
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Should Thyroid-Like Follicular RCC be Recognized as a Distinctive Entity at this time?

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
DIFFERENTIAL DIAGNOSIS OF EOSINOPHILIC/ONCOCYctic RENAL NEOPLASMS

Papillary Renal Cell Carcinoma, Type 2
Oncocytoma
Eosinophilic Chromophobe Carcinoma
“Papillary renal cell carcinoma with oncocytic cells”
Tubulocystic renal cell carcinoma
Renal Cell Carcinoma, Unclassified
Angiomyolipoma
If focal (<5%) urothelial carcinoma (non-invasive or invasive) is present in an otherwise classic collecting duct carcinoma, the diagnosis should be:

1. Collision tumor between collecting duct carcinoma and UC
2. Collecting duct carcinoma with focal urothelial differentiation
3. Urothelial carcinoma with prominent glandular differentiation
4. Unclassified carcinoma
5. No opinion or insufficient experience with entity
What percent of a tumor needs to be classic collecting duct carcinoma when associated with undifferentiated carcinoma in order to diagnose as collecting duct carcinoma as opposed to unclassified carcinoma?

1. >10%
2. >50%
3. >90%
4. 100%
5. Not sure or insufficient experience with entity
Denote AMLs with epithelioid morphology as “epithelioid AMLs” which are then divided into epithelioid AMLs without and with atypia, the latter category associated in the literature with malignant potential.

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Assess prognosis in epithelioid AMLs based on published criteria into low, intermediate, and high risk of malignant behavior as opposed to denoting as benign or malignant.

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Differential Diagnosis of Cystic Renal Neoplasms

- Clear cell renal cell carcinoma with prominent cysts
- Clear cell renal cell carcinoma arising in a simple cysts
- Multilocular cystic renal cell carcinoma

- Cystic Nephroma/Mixed Epithelial and Stromal Tumor
- Synovial sarcoma („Cystic embryonal sarcoma“)
- Cystic partially differentiated nephroblastoma
- Tubulocystic carcinoma
- Renal cancer in end stage renal disease
Mixed Epithelial and Stromal Tumor
smaller cysts with phyllodes glands pattern and stromal luteinization more common in MEST
large cysts, thin septae and low stromal to epithelial ratio more common in CN

"renal epithelial and stromal tumor" (REST)
Are Cystic Nephroma and Mixed Epithelial and Stromal Tumor a Single Entity?

Arguments against a single entity:

History
Grossly look different
Microscopically look different
Immunohistochemical similarities not specific
Demographic similarities not specific
Are Cystic Nephroma and Mixed Epithelial and Stromal Tumor a Single Entity?

Arguments for a single entity

Some mixed epithelial and stromal tumors have areas which grossly and microscopically resemble cystic nephroma

Both occur predominantly in women

Immunohistochemical similarities
Do you consider CN and MEST variations on the same lesion, or different lesions?

1. CN and MEST are variations on the same lesion
2. CN and MEST are distinct lesions
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
If you consider CN and MEST variations on the same lesion, what name will you use for them?

1. CN/MEST
2. MEST
3. Renal epithelial and stromal tumor (REST)
4. Other
Tubulocystic RCC
Should Tubulocystic-RCC be recognized as an entity at this time?

1. Yes  
2. No  
3. Uncertain even with personal experience/knowledge  
4. Not enough personal experience/knowledge
## Challenges for Pathologists

<table>
<thead>
<tr>
<th>Diagnostic Marker</th>
<th>Novel Tumor Entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Marker</td>
<td>Correct Staging?</td>
</tr>
<tr>
<td></td>
<td>Relevant Grading?</td>
</tr>
<tr>
<td>Predictive Marker</td>
<td>Are there any?</td>
</tr>
</tbody>
</table>
Prognosis

• Type

• Stage

• Grade

• Other
Sporadic Renal Cell Carcinoma

Moch et al., Cancer 2000
Papillary renal cell carcinoma

Type 1

Type 2
Definition Adenoma

• Tumours with papillary or tubular architecture of low nuclear grade and 5 mm in diameter or smaller

• While grade 1 papillary tumours between 0.5 cm and 2 cm are strictly defined as carcinomas, many pathologists prefer to report them as „papillary epithelial neoplasms of low malignant potential“ for practical reasons
Differential Diagnosis: metanephric adenoma vs. papillary adenoma/carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Metanephric adenoma</th>
<th>Papillary adenoma/carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomeruloid bodies</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>Necrosis</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>Psammoma bodies</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+/-</td>
<td>-/+</td>
</tr>
<tr>
<td>EMA</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leu-7 (CD57)</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Type and Prognosis of Papillary Renal Cancer

Moch et al.: Cancer 89, 2000
The distinction between type 1 versus type 2 papillary RCC harbors a prognostic value:

1. Yes
2. No

73%
27%
How do you subtype papillary renal cell carcinoma?

1. type 1 vs type 2
2. type 1 vs type 2 vs type 3 [oncocytic]
3. type 1 vs type 2a vs type 2b vs type 2c (based on molecular classification)
4. Fuhrman grading
5. Other
Should Oncocytic Papillary-RCC be recognized as a separate entity at this time?

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Hereditary Leiomyomatosis and RCC Syndrome (HLRCC)

Fumarate Hydratase (\(FH\)-) Gene on 1q42
Leiomyomas of the Skin
Should HLRCC be Recognized as a Distinctive Entity at this time?

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge
Fuhrman Grading in RCC

Cancer-specific mortality-free rates

I (n = 20) II (n = 197) III (n = 162) IV (n = 52)

- 2-year: 100.0% 95.9% 80.2% 38.5%
- 5-year: 95.0% 88.8% 60.5% 26.9%
- 10-year: 89.4% 83.3% 56.4% 11.5%

II vs. I (log-rank P = 0.497)
III vs. I (log-rank P = 0.010)
IV vs. I (log-rank P < 0.001)

Duration of follow-up, months

Hong SK, BJUI 2010
Grading of Chromophobe RCC


How should we grade clear cell RCC?

1. Fuhrman
2. Nucleolar
How should we grade papillary RCC?

1. Fuhrman
2. Nucleolar
3. Collapsed nucleolar
How should we grade chromophobe RCC?

1. None
2. Fuhrman
3. Chromophobe grade (Paner et al)
4. Nucleolar
Unlike the Skywalker family, once the carcinoma cell has gone over to the dark side, we cannot determine its ancestor.
For Sarcomatoid Tumors Do You Report the Underlying Subtype

1. Yes
2. No

Bar chart showing 94% for Yes and 6% for No.
Prognostic Relevance of Sarcomatoid Differentiation in clear cell RCC

Sarcomatoid RCC is not an own tumor entity!

Moch et al.: Cancer 2000
Do You Consider a Tumor Area Sarcomatoid?

1. If it shows early sarcomatoid change
2. If it has a spindle cell pattern
3. If it is very atypical and resembles any type of sarcoma
4. If it is very atypical and resembles any type of sarcoma even without a spindle cell morphology
If a Tumor Shows Sarcomatoid Morphology Only, Do You Classify as (more than one alternative may be specified)

1. Unclassified carcinoma
2. Unclassified carcinoma with a sarcomatoid component
3. Fuhrman grade 4
4. 2 & 3
Tumor Staging
Tumor Staging


When invasion of the renal sinus is uncertain at least 3 blocks of the tumor – renal sinus interface should be submitted. If invasion is grossly evident, or obviously not present (small peripheral tumor) only one block is needed to confirm the gross impression:

1. Agree
2. Disagree
For staging purposes, do you consider renal sinus invasion (pT3a) to be present when the sections show involvement of any endothelial lined spaces within the renal sinus regardless of size?

1. Yes
2. No

10% 90%
Should the presence or absence of tumor necrosis be routinely included as a component of a RCC pathology report evaluation?

1. Yes
2. No
Should the component of necrosis be recorded as a percentage of the total tumor area?

1. Yes
2. No
Should any assessment of amount (percentage) of necrosis be derived by:

1. MACROSCOPIC EVALUATION
2. MICROSCOPIC EXAMINATION OF SECTIONS
3. BOTH
Challenges for Pathologists

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</tr>
<tr>
<td>Predictive Marker</td>
<td>Are there any?</td>
</tr>
</tbody>
</table>
ISUP Consensus Conference

Vancouver (USCAP)

Working Group IV

(Biomarker: Diagnosis, Prognosis, Prediction)

**Group Chair** Holger Moch, **Co-chair** Liang Cheng,

**Rapporteur** Steven Shen,

**Members:** Victor Reuter, Nathalie Leclercq-Roux, Maria Merino, George Netto, Puay Hoon Tan
A proposed marker-based strategy design to evaluate predictive biomarkers.

Pal S K et al. Mol Cancer Ther 2010;9:3115-3125
Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma

VHL and tumor development

Frew and Krek, 2008
Chemokine receptor CXCR4 downregulated by von Hippel–Lindau tumour suppressor pVHL!

VHL<sup>-/-</sup> with strong CXCR4 expression

Staller et al. Nature 2003
<table>
<thead>
<tr>
<th>Current Prognostic Parameters in ccRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors:</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Pathologic factors:</td>
</tr>
<tr>
<td>pTNM</td>
</tr>
<tr>
<td>Histologic type</td>
</tr>
<tr>
<td>Fuhrman grade</td>
</tr>
<tr>
<td>LVI</td>
</tr>
<tr>
<td>Tumor necrosis</td>
</tr>
<tr>
<td>Clinical factors:</td>
</tr>
<tr>
<td>ECOG performance status</td>
</tr>
<tr>
<td>Hgb level</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emerging Potential Molecular Prognostic and Predictive Parameters in ccRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia inducible:</td>
</tr>
<tr>
<td>HIF1</td>
</tr>
<tr>
<td>CAIX</td>
</tr>
<tr>
<td>CAXII</td>
</tr>
<tr>
<td>CXCR4</td>
</tr>
<tr>
<td>VEGF/VEGFR1/VEGFR2/R</td>
</tr>
<tr>
<td>ILGF1</td>
</tr>
<tr>
<td>Cell adhesion markers:</td>
</tr>
<tr>
<td>EpCAM</td>
</tr>
<tr>
<td>E-cadherin</td>
</tr>
<tr>
<td>z-Catenin</td>
</tr>
<tr>
<td>Catenin-6</td>
</tr>
<tr>
<td>Proliferation markers:</td>
</tr>
<tr>
<td>Ki-67</td>
</tr>
<tr>
<td>MCM2</td>
</tr>
<tr>
<td>Cell cycle regulators:</td>
</tr>
<tr>
<td>Cyclin</td>
</tr>
<tr>
<td>p27</td>
</tr>
<tr>
<td>Apoptosis regulators:</td>
</tr>
<tr>
<td>p53</td>
</tr>
<tr>
<td>Bcl2</td>
</tr>
<tr>
<td>Smac/DIABLO</td>
</tr>
<tr>
<td>mTOR pathway</td>
</tr>
<tr>
<td>PTEN</td>
</tr>
<tr>
<td>Akt</td>
</tr>
<tr>
<td>Phos S6k aks</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; LVI, lamina propria invasion.
### Randomised studies in the first line setting in metastatic clear cell renal cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>MSKCC risk groups</th>
<th>Study drug vs control arm</th>
<th>Progression-free survival (months)</th>
<th>Overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer et al, 2007</td>
<td>Clear cell</td>
<td>All</td>
<td>Sunitinib vs interferon</td>
<td>11 vs 5</td>
<td>26.4 vs 21.8</td>
</tr>
<tr>
<td>Hudes et al, 2007</td>
<td>All types</td>
<td>Poor</td>
<td>Temsirolimus vs interferon</td>
<td>5.5 vs 3.1</td>
<td>10.9 vs 7.3</td>
</tr>
<tr>
<td>Escudier et al, 2007</td>
<td>Clear cell</td>
<td>All</td>
<td>Bevacizumab + interferon</td>
<td>10.2 vs 5.4</td>
<td>22.9 vs 20.6</td>
</tr>
<tr>
<td>Rini et al, 2008</td>
<td>Clear cell</td>
<td>All</td>
<td>Bevacizumab + interferon</td>
<td>8.5 vs 5.1</td>
<td>18.3 vs 17.4</td>
</tr>
<tr>
<td>Sternberg et al, 2009</td>
<td>Clear cell</td>
<td>All</td>
<td>Pazopanib vs placebo</td>
<td>11.1 vs 2.8</td>
<td>NA</td>
</tr>
</tbody>
</table>
Agents such as sunitinib act through a multitude of mechanisms, yielding numerous potential biomarkers of response.
von Hippel-Lindau Gene Status and Response to Vascular Endothelial Growth Factor Targeted Therapy for Metastatic Clear Cell Renal Cell Carcinoma

VHL-Mutation ↔ Gene expression

Banks, R.E.et al.; Cancer Res 2006: Correlation of VHL Mutation type with gene expression
VHL Mutation in clear cell renal cancer

Driver and Passenger VHL Mutations

3 different groups of missense mutations:

1) severe destabilization of pVHL

2) without destabilizing effects on pVHL but relevance for the interaction with HIFα, elongin B, and elongin C

3) pVHL functions comparable with wild type.

Thank you
Differential Diagnosis of Renal Cell Carcinoma - Immunohistochemical and Molecular Markers

Holger Moch
Department Pathology
University Hospital Zurich
Review – Kidney Cancer

Renal Tumor Biopsies for Evaluation of Small Renal Tumors: Why, in Whom, and How?

Mesut Remzi, I. Michael Marberger
Department of Urology, Medical University of Vienna, Vienna, Austria

Renal mass sampling: An enlightened perspective
Mary K Samplaski,1 Ming Zhou,2 Brian R Lane,1 Brian Herts,1 and Steve C Campbell1
1Glickman Urological and Kidney Institute, 2Pathology and Laboratory Medicine Institute, and 3Imaging Institute, Cleveland Clinic, Cleveland, Ohio, and 4Division of Urology, Spectrum Health Hospital System, Grand Rapids, Michigan, USA

Review Articles

Renal Mass Biopsy—A Renaissance?
Brian R. Lane, Mary K. Samplaski, Brian R. Herts, Ming Zhou, Andrew C. Novick and Steven C. Campbell*
From the Glickman Urological Institute (BRL, MKS, ACN, SCC) and Departments of Radiology (BRL) and Anatomic Pathology (MK), Cleveland Clinic, Cleveland, Ohio
Potential of Needle Biopsy

• Diagnostic accuracy increases
  – Before 2001: 82%
  – 2001-2006: 90%
  – 2010: >95%

• Non-informative biopsies: 10-20%

• „oncocytic neoplasm“: diagnostic dilemma?

• Metastases of RCC !!
# Renal Tumors with Eosinophilic Cytoplasm

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clear Cell RCC, Eosinophilic</th>
<th>Chromophob RCC, Eosinophilic</th>
<th>Oncocytoma</th>
<th>MiTF/TFE Translocation-associated Carc.</th>
<th>Epithelioid Angiomyolipoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>+/-</td>
<td>- (rarely +)</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>RCC</td>
<td>+</td>
<td>-/+</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CK7</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EpCAM</td>
<td>V</td>
<td>+</td>
<td>-/+</td>
<td>V</td>
<td>-</td>
</tr>
<tr>
<td>TFE3/TFEB</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Melan-A, HMB45</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ in TFEB carcinoma</td>
<td>+</td>
</tr>
<tr>
<td>CAIX</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
# Hereditary Renal Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Protein</th>
<th>Chromosome</th>
<th>Kidney</th>
<th>Skin</th>
<th>Other Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau</td>
<td>VHL, pVHL</td>
<td>3p25</td>
<td>Multiple, bilateral clear-cell renal cell carcinoma (CCRCC), renal cysts</td>
<td>-</td>
<td>Retinal and CNS haemangioblastomas, phaeochromocytoma, pancreatic cysts</td>
</tr>
<tr>
<td>Hereditary papillary renal cancer</td>
<td>c-MET, HGF-R</td>
<td>7q31</td>
<td>Multiple, bilateral papillary renal cell carcinomas (PRCC), Type 1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and RCC</td>
<td>FH, FH</td>
<td>1q42-q43</td>
<td>Papillary renal cell carcinoma (PRCC), non-Type 1</td>
<td>Nodules (leiomyomas)</td>
<td>Uterine leiomyomas and leiomyosarcomas</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé</td>
<td>BHD, Folliculin</td>
<td>17p11.2</td>
<td>Multiple chromophobe RCC, conventional RCC, hybrid oncocytoma, papillary RCC, oncocytic tumors</td>
<td>Facial fibrofolliculomas</td>
<td>Lung cysts, spontaneous pneumothorax</td>
</tr>
<tr>
<td>Constitutional chromosome 3 translocation</td>
<td>unknown</td>
<td>unknown</td>
<td>Multiple, bilateral clear-cell renal cell carcinomas (CCRCC)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperparathyroidism-jaw tumor (HP-JT)</td>
<td>HRT2P</td>
<td>1q25-q32</td>
<td>Mixed epithelial and stromal tumors, papillary RCC: cysts</td>
<td>-</td>
<td>Parathyroid tumors, fibro-osseous mandibular and maxillary tumors</td>
</tr>
<tr>
<td>Familial papillary thyroid cancer (FPTC)</td>
<td>Unknown gene</td>
<td>1q21</td>
<td>Papillary RCC, oncocytoma</td>
<td>-</td>
<td>Papillary thyroid cancer, nodular thyroid disease</td>
</tr>
</tbody>
</table>
Birt Hogg Dubé syndrome
How should HOCT be recognized?

1. Subcategory of oncocytooma
2. Subcategory of chromophobe
3. As a distinctive entity
4. Should not be recognized
5. I’m not sure
Are the hybrid tumors associated with Birt Hogg Dube syndrome distinct?

1. No, hybrid tumors associated with Birt Hogg Dube syndrome are not distinct.
2. Yes, all hybrid tumors associated with BHD syndrome have distinct morphology.
3. Yes, but one should rule out the possibility of “sporadic” hybrid tumor or tumor associated with oncocytosis.
4. There is not enough experience to resolve this problem at the moment.
Novel renal tumor types with clear cytoplasm

• Translocation carcinoma

• Renal Cancer in End Stage Renal Disease
  – ACD-related RCC
  – Clear cell and papillary RCC in ESRD

• Sporadic clear cell and papillary and cystic (!) renal cancer

• Leiomyomatous renal cancer

• Multilocular cystic renal cell carcinoma

• Angiomyolipoma / Epitheloid Angiomyolipoma
For distinguishing clear cell RCC from chromophobe RCC, do you use the following markers?

1. Both CD117 & CAIX
2. CAIX
3. CD117
4. CK7
5. Hale’s colloidal iron
# Renal Tumors with Clear Cytoplasm

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clear Cell RCC</th>
<th>Chromophobe RCC</th>
<th>MITF/TFE Translocation-associated Carcinoma</th>
<th>Clear Cell Papillary RCC</th>
<th>Epitheloid Angiomyolipoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>-</td>
<td>+ (cell cluster)</td>
<td>-</td>
<td>+ (diffuse)</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
<td>- / (rarely +)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
<td>- (rarely +)</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>PAN-CK</td>
<td>+</td>
<td>+</td>
<td>- (rarely +)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CAIX</td>
<td>+</td>
<td>- (+ perinecrotic areas)</td>
<td>- (+ in some cases)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>TFE3/TFEB</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melan-A, HMB-45</td>
<td>-</td>
<td>-</td>
<td>+ in TFEB carcinoma, rarely + in TFE3</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Clear Cell Renal Cancer

VHL Deletion (FISH): 69%
(Cancer Res 1998)
CA IX and Tumor Development

Carcinogenesis

- Hypermethylation of CA9 gene
  - Demethylation

- CA IX expression

- Mutation -> Tumor
Early on in VHL disease, the vast majority of lesions in kidneys of VHL patients are single cells, cysts occur relatively infrequent and carcinoma less frequently still.

anti-CA9 (HIF target gene)
Distinct tumor suppressor mechanisms of pVHL that may contribute to renal tumorigenesis

- Activation of transcription
  - metabolism
  - proliferation
  - angiogenesis
  - invasion
  - metastasis

Staller et al., Nature 2003

- MT dynamic instability
  - Migration
  - Mitosis

Maintenance of the primary cilium

Thoma, C. Nat Cell Biol 2009
Is loss of VHL sufficient to cause tumors?

W.Y. Kim, W.G. Kaelin, 2004
Kidney-specific Vhlh/Pten knockout

<table>
<thead>
<tr>
<th>A</th>
<th>Ksp-Cre</th>
<th>Vhlh</th>
<th>Pten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- pos</td>
<td>fl/fl</td>
<td>fl/fl</td>
</tr>
<tr>
<td></td>
<td>+/+</td>
<td>+/+</td>
<td>fl/fl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Ksp-Cre</th>
<th>Vhlh</th>
<th>Pten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- pos</td>
<td>fl/fl</td>
<td>fl/fl</td>
</tr>
<tr>
<td></td>
<td>+/+</td>
<td>fl/fl</td>
<td>fl/fl</td>
</tr>
</tbody>
</table>

Frew I. et al. EMBO J 2008
Inside the primary cilium

Kidney tubule

Axoneme
(9+0 microtubule doublets)

IFT (Intraflagellar transport complex)
- Kinesin II
- Dynein-1b
- Cargo (e.g., Par3, Par6, PKC)

Receptors, channels

Transition fibres

Basal body
pVHL localizes to primary cilia in mouse kidney tubules
Additional mutation in VHL-/- cells that lead to cilia loss

Cyst-independent pathway in sporadic disease

Cyst-dependent pathway in VHL disease

Additional mutation in VHL-/- cells that lead to proliferation

Additional mutation in cyst wall cells that lead to proliferation

Hifα

GSK3β

VHL loss

= tubular epithelial cell

= Carbonic anhydrase IX overexpressing tubular epithelial cell

= cyst wall cell

= carcinoma cell

PTEN?
Multilocular cystic renal cell carcinoma
Is it Acceptable for MC-RCC to have Fuhrman Grade 2 Nuclei?

1. Yes
2. No
3. Uncertain even with personal experience/knowledge
4. Not enough personal experience/knowledge

78% Yes
20% No
2% Uncertain even with personal experience/knowledge
1% Not enough personal experience/knowledge
What terminology for a multicystic renal neoplasm with minute areas of bland clear cells in the septa?

1. Multilocular cystic renal cell carcinoma
2. Multilocular cystic renal cell neoplasm of low malignant potential
3. Renal cell carcinoma with extensive cystic change
4. Multicystic renal epithelial neoplasm with focal clear cell change
5. None of the above or Uncertain
Renal Cyst in ADPKD

Ki-67
In the setting of acquired cystic disease or sporadically, what do you call cysts like this with proliferative epithelium?

1. Atypical cysts
2. Cysts with epithelial proliferation
3. Other term
4. Uncertain; not enough experience
Novel renal tumor types with clear cytoplasm - Subgroups of clear cell RCC?

- Translocation carcinoma

- Renal Cancer in End Stage Renal Disease
  - ACD-related RCC
  - Clear cell and papillary RCC in ESRD

- Sporadic clear cell and papillary and cystic (!) renal cancer

- Leiomyomatous renal cancer

- Multilocular cystic renal cell carcinoma
„Translocation“ Type of Renal Cancer in Children

no VHL-Mutations!
Primary Renal Neoplasms with the ASPL-TFE3 Gene Fusion of Alveolar Soft Part Sarcoma

A Distinctive Tumor Entity Previously Included among Renal Cell Carcinomas of Children and Adolescents

TFE3-Proteine-Expression
„Translocation“ Type of Renal Cancer in Children

Xp11 Translocation Renal Cell Carcinoma in Adults: Expanded Clinical, Pathologic, and Genetic Spectrum

Pedram Argani, MD,* † Semra Olgac, MD,‡ Satish K. Tickoo, MD,‡ Michael Goldfischer, MD,§ Holger Moch, MD,∥ David Y. Chan, MD,* ′ John N. Eble, MD,# Stephen M. Bonsib, MD,# Mireya Jimeno, MD,** Josep Lloreta, MD, PhD, † † Athanase Billis, MD, ‡ ‡ Jessica Hicks, BA,* ′ ′ Angelo M. De Marzo, MD, PhD,* † † Victor E. Reuter, MD,‡ and Marc Ladanyi, MD‡

- 14/28 pts: Stage 4
- 11/13 pts: pN1
- 5/6 pts developed hematogenous metastases

- Xp11 Translocation Carcinoma in Adults are Aggressive Cancers
Translocation Carcinomas (MiTF/TFE Transcription Factor Family)

Xp11.2:

*ASPL-TFE3* Renal Carcinomas t(X;17)

*PRCC-TFE3* Renal Carcinomas t(X;1)

*Other TFE3* Renal Carcinomas (*PSF-, NonO-, CLTC*)

*t(6;11):* TFEB Renal Carcinomas

MiTF: Malignant Melanoma

TFEC: ?
Should t(6;11) RCC be Recognized as an Entity at this time?

1. Yes, include it with Xp11 RCC under MiT Family Translocation RCC
2. Yes, make it its own category
3. No
4. Uncertain even with personal experience/knowledge
5. Not enough personal experience/knowledge
When should TFE3 and TFEB analysis (IHC and/or FISH) be requested to identify translocation RCC cases?

1. When RCC is diagnosed in a patient under 30 years of age
2. When the morphology is suggestive of translocation RCC in a patient older than 30 year of age
3. Both A and B
4. I do not request for TFE3 or TFEB immunostaining
When a translocation carcinoma is suspected, when should FISH for TFE3 or TFEB be requested?

1. It should almost always be requested when a translocation RCC is suspected.
2. It should be requested only for cases with histologic features of translocation RCC but with negative or equivocal TFE3/TFEB immunostaining.
3. It should be requested only for cases with positive TFE3/TFEB immunostaining to confirm the IHC.
4. Both B and C.
5. I do not request for this test.
Clear cell-papillary RCC, sporadic (!)

Clear Cell Papillary Renal Cell Carcinoma
A Distinct Histopathologic and Molecular Genetic Entity

Stefano Gobbo, MD,* † John N. Eble, MD,* David J. Grignon, MD,* Guido Martignoni, MD,† Gregory T. MacLennan, MD,‡ Rajal B. Shah, MD,§ Shaobo Zhang, MD,* Matteo Brunelli, MD,† and Liang Cheng, MD*
Spectrum of Epithelial Neoplasms in End-Stage Renal Disease

An Experience From 66 Tumor-Bearing Kidneys With Emphasis on Histologic Patterns Distinct From Those in Sporadic Adult Renal Neoplasia

Satish K. Tickoo, MD,† Mariza N. dePeralta-Venturina, MD,‡ Lana R. Harik, MD,*, Heath D. Worcester, MD,§ Mohamed E. Salama, MD,† Andrew N. Young, MD,§ Holger Moch, MD,‖ and Mahul B. Amin, MD§
Leiomyomatous Renal Cell Carcinoma
Differential Diagnosis of Cystic Renal Neoplasms

- Clear cell renal cell carcinoma with prominent cysts
- Clear cell renal cell carcinoma arising in a simple cysts
- Multilocular cystic renal cell carcinoma
- Cystic Nephroma/Mixed Epithelial and Stromal Tumor
- Synovial sarcoma („Cystic embryonal sarcoma“)
- Cystic partially differentiated nephroblastoma
- Tubulocystic carcinoma
- Renal cancer in end stage renal disease
Are Cystic Nephroma and Mixed Epithelial and Stromal Tumor a Single Entity?

Arguments against a single entity:

History
Grossly look different
Microscopically look different
Immunohistochemical similarities not specific
Demographic similarities not specific
Are Cystic Nephroma and Mixed Epithelial and Stromal Tumor a Single Entity?

Arguments for a single entity

Some mixed epithelial and stromal tumors have areas which grossly and microscopically resemble cystic nephroma

Both occur predominantly in women

Immunohistochemical similarities
smaller cysts with phyllodes glands pattern and stromal luteinization more common in MEST
large cysts, thin septae and low stromal to epithelial ratio more common in CN

"renal epithelial and stromal tumor" (REST)
## Renal Tumors with Papillary Architecture

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Papillary RCC</th>
<th>Collecting Duct Carcinoma</th>
<th>Metanephric Adenoma</th>
<th>Mucinous Tubular and Spindle Cell Carcinoma</th>
<th>Clear Cell Papillary RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>+ (often luminal pattern)</td>
<td>-</td>
<td>-</td>
<td>-/+ (focal)</td>
<td>-</td>
</tr>
<tr>
<td>RCC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>V</td>
<td>-/+</td>
</tr>
<tr>
<td>WT1</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD57</td>
<td>-</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>ULEX-1</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
</tbody>
</table>
## Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>MTSC (%)</th>
<th>Papillary Type 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMACR</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>RCC</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>CD10</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>c-kit</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>HMWK</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>CK7</td>
<td>81</td>
<td>65</td>
</tr>
<tr>
<td>EMA</td>
<td>95</td>
<td>88</td>
</tr>
</tbody>
</table>
In the absence of classical histology can MTS-RCC be definitely distinguished from PRCC?

1. Yes by morphology
2. Yes by morphology and immunostains
3. Yes by morphology and absence of trisomy 7, 17
4. Uncertain even with personal experience/knowledge
5. Not enough personal experience/knowledge
Which IHC marker do you think is the most useful in confirming renal primary?

1. CK7
2. **Pax 2** and/or Pax 8
3. CD10
4. RCC marker
5. AMACR (P504)
transcription factor, up-regulated in nephrogenesis
 silenced in mature proximal and distal tubular epithelium
 mechanisms of reactivation unclear
PAX2 expression pattern in 16 sporadic ccRCC patients.

A, Western blot analysis of HK-2 cells grown under normoxia (N) and hypoxia (H). β-Actin was used as a loading control.

PAX2 expression and overall survival in ccRCC patients.


p-value for logrank test < 0.0001
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Spindle Cells in RCC</th>
<th>Mucinous Tubular and Spindle Cell Carcinoma</th>
<th>Sarcoma (focal in leiomyosarcoma)</th>
<th>Angiomyolipoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-CK (AE1/AE3)</td>
<td>+ may be focal</td>
<td>+</td>
<td>- (focal in leiomyosarcoma)</td>
<td>-</td>
</tr>
<tr>
<td>Desmin</td>
<td>- (rarely focal +)</td>
<td>-</td>
<td>+ in myosarcomas</td>
<td>+</td>
</tr>
<tr>
<td>Actin-sm</td>
<td>- (rarely focal +)</td>
<td>-</td>
<td>+ in myosarcomas</td>
<td>+</td>
</tr>
<tr>
<td>CD99</td>
<td>-</td>
<td>-</td>
<td>+ in synovial sarcoma</td>
<td>V</td>
</tr>
<tr>
<td>Melan-A (HMB45)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CK7</td>
<td>-/(rarely focal +)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CAIX</td>
<td>+ (usually)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Tumors with Spindle Cell Morphology

<table>
<thead>
<tr>
<th>Antibody</th>
<th>RCC, unclassified</th>
<th>Collecting Duct Carcinoma</th>
<th>Urothelial Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK20</td>
<td>-</td>
<td>- (rarely focal +)</td>
<td>+/-</td>
</tr>
<tr>
<td>p63</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>RCC</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>+/-</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>CK5/6</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>CK17</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Ulex-1</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Which marker do you use most frequently in the workup of a sarcomatoid RCC?

1. Broad spectrum keratins
2. PAX2/PAX8
3. CK7 and CK20
4. CD10
5. CAIX
6. I do not use any markers to make this diagnosis
# Small Blue Round Cell Tumors of Kidney

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Wilms tumor</th>
<th>Ewing Sarcoma/PNET</th>
<th>Small Cell Carcinoma</th>
<th>Lymphoma</th>
<th>Synovial Sarcoma, Poorly Differentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FLI-1</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD99</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>CD45 (LCA)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Desmin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PAN-CK (AE1/AE3)</td>
<td>+ (in tubules)</td>
<td>+/- (focal)</td>
<td>+ (often dot-like)</td>
<td>-</td>
<td>-/-</td>
</tr>
</tbody>
</table>
Primary Renal Synovial Sarcoma

Immunophenotype:
- EMA +
- CD56 +
- CD99 +/-
- CD34 -
- Desmin -
- Actin -
- Cytokeratin -
SYT-SSX Fusion from translocation t(X;18)
Ewing-Sarcoma/PNET

CD 99
Renal carcinoid from a horseshoe kidney
Synaptophysin
DD „Small round blue“ cell tumors in the kidney

- blastemal prominent Wilms tumor
- lymphoma
- clear cell sarcoma
- small cell carcinoma
- monophasic synovial sarcoma
- PNET/Ewing sarcoma
- neuroblastoma
- desmoplastic round cell tumor
Table 1.01
Immunohistochemical differentiation of neuroectodermal tumours from other tumours with similar microscopic features.

<table>
<thead>
<tr>
<th></th>
<th>VIM</th>
<th>CK</th>
<th>CHR</th>
<th>SYN</th>
<th>NSE</th>
<th>CD99</th>
<th>CD45</th>
<th>WT-1</th>
<th>CD117</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNET-EWS</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>NB</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>NEC</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>NHL</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Blastemal WT</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: PNET-EWS = primitive neuroectodermal tumour / Ewing sarcoma, NB = neuroblastoma, NEC = neuroendocrine carcinoma, NHL = non-Hodgkin lymphoma, WT = Wilms tumour, VIM = vimentin, CK = cytokeratin, CHR = chromogranin, SYN = synaptophysin, NSE = neuron specific enolase.

* CD99 is expressed by lymphoblastic lymphoma.
The future has arrived

"Here's my sequence..."

New Yorker
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,

Single-Cell Exome Sequencing Reveals Single-Nucleotide Mutation Characteristics of a Kidney Tumor

Xun Xu,1,2,14 Yong Hou,1,3,14 Xuyang Yin,1,14 Li Bao,1,14 Aifa Tang,5,6,14 Luting Song,1 Fuqiang Li,1 Shirley Tsang,7 Kui Wu,1 Hanjie Wu,1,8 Weiming He,1 Liang Zeng,1 Manjie Xing,1 Renhua Wu,1 Hui Jiang,1 Xiao Liu,1 Dandan Cao,

VHL and Deep Sequencing

- several low frequency single nucleotide variants
- different VHL mutations: 2 independent clonal expansions-parallel somatic evolution of primary-and mets (Gerstung M. et al.; Nature Comm; May 2012)
Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma

Ignacio Varela¹, Patrick Tarpey¹, Keiran Raine¹, Dachuan Huang², Choon Kiat Ong³, Philip Stephens¹, Helen Davies¹, David Jones¹, Meng-Lay Lin¹, Jon Teague¹, Graham Bignell¹, Adam Butler¹, Juok Cho¹, Gillian L. Dalglish¹, Danushka Galappaththige¹, Chris Greenman¹, Claire Hardy¹, Mingming Jia¹, Callie Latimer¹, King Wai Lau¹, John Marshall¹, Stuart McLaren¹, Andrew Menzies¹, Laura Mudie¹, Lucy Stebbings¹, David A. Largaespada³, L. F. A. Wessels⁴, Stephane Richard⁵, Richard J. Kahnoski⁶, John Anema⁷, David A. Tuveson⁸, Pedro A. Perez-Mancera⁸, Ville Mustonen⁹, Andrej Fischer¹⁰, David J. Adams¹¹, Alistair Rust¹¹, Waraporn Chen-on¹, Chutima Subimerb¹, Karl Dykema¹², Kyle Purge¹², Peter J. Campbell¹, Bin Tean Teh¹²,¹³,¹⁴, Michael R. Stratton¹,¹⁵ & P. Andrew Futreal¹
Polybromo-1 (BAF180) in ccRCC


Nucleosome/Histone/Chromatin Remodeling Complexes

~40% ccRCC mutated in PBRM1!

Loss of PBRM1 expression is correlated with tumor stage, grade and survival

Rafal Pawłowski et al., Int J Cancer, 2012
VHL-loss derived glycoproteome & its use for a diagnostic serum signature in renal cancer

wt versus VHL-/- cells
Cell Surface Capturing Proteomics: N-linked Glycoproteins

pVHL-negative vs. positive 786-O cells: 272 cell surface proteins
Quantitative MS: 44 proteins pVHL-dependent
VHL and a Serum Screening Test for Clear Cell Renal Cancer

- N-glycosylated proteins detectable in serum

Boysen et al. Neoplasia 2012
Conclusions

• Renal mass biopsy - a renaissance!

• Subtype specific clinical trials!
• Current grading system useful?

• Predictive marker - Relevance of Driver Mutations
  • different groups of VHL mutations with/without PBRM1 alterations might have different predictive impact

• Multi-regional analyses required for therapeutic outcome prediction