Goals:

to analyze
(i) congenital abnormalities
(ii) cystic lesions
(iii) kidney tumors


Objectives:
• identify the most common congenital abnormalities affecting kidneys
• identify the most common cystic lesions
• contrast and compare the most common cystic lesions in children versus adults
• identify the most common malignant tumor in adults
• identify the most common malignant tumor in children
• contrast & compare malignant tumors in adults versus in children
Development
Congenital abnormalities

Kidney development – 3 stages: pro-, meso-, metanephros
think “U” turn

Promaturation
4th week
Mesonephric duct & tubules
Metanephros
Mesoepithelial duct canal, in contact with cloaca, it grows cranially as ureteric bud
Ureteric bud and metanephros reciprocally induce growth forming kidney

5
kidneys “ascend” from pelvis to upper retroperitoneum (6-9 weeks)

Congenital abnormalities
10% born with potentially significant malformations

CAKUT: congenital anomalies of the kidney and urinary tract

• Agenesis = absence, bilateral or unilateral
• Hypoplasia = small size
• Ectopic = abnormal location, pelvis
• Horseshoe = fused kidneys
  • common 1:500-1000 autopsies
  • lower > upper pole

Adrenal gland
Kidney
Ureter
Bladder

Inferior mesenteric artery

Adrenal gland
Renal cystic diseases

Multicystic renal dysplasia
Childhood Autosomal Recessive Polycystic Kidney Disease – ARPKD
Adult Polycystic Kidney Disease – APKD
Medullary diseases with cysts
Acquired (dialysis-associated) cystic disease
Simple cysts

Multicystic renal dysplasia:

1. Typical presentation:
   - stillbirth if bilateral, unilateral/segmental, - depends on associated abnormalities, ureteropelvic obstruction
3. Etiology/pathogenesis: sporadic
   Developmental abnormality NOT related to neoplasia
4. Pathology:
   - kidney(s) enlarged, irregular shape, "bunch of grapes"
   - unilateral, segmental or bilateral
   - disorganized renal cortex, "bunch of grapes"
   - associated abnormalities: ureteropelvic junction obstruction, ureteral agenesis/atrophy
5. Tests: radiology
6. Prognosis: bilateral not compatible with life, depends on associated abnormalities
7. Treatment: no treatment available, observation

Multicystic renal dysplasia - pathology

- noncommunicating cysts of varying size
- separated by dysplastic parenchyma: disorganized renal parenchyma with persistence of immature tubules, surrounded by collars of condensed mesenchyme, cartilage
- absence of a normal pelvocaliceal system
- associated with unilateral or ureteropelvic atresia (closed passage)
Kidneys and lungs

- Bilateral agenesis, bilateral dysplasia
- Absence of in utero urine production leads to oligohydramnios (decreased amniotic fluid)
- Hypoplastic lungs
- Potter’s syndrome…

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**Kidney and lung abnormalities**

- Potter sequence (aka Potter’s syndrome): lung hypoplasia
- Flat face with low set ears, extremities developmental defects

**INCOMPATIBLE WITH LIFE**

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**Childhood Autosomal Recessive Polycystic Kidney Disease –ARPKD**

1. Typical presentation: renal, liver failure
   - perinatal, neonatal, infantile, juvenile subcategories

2. Epidemiology:
   - rare, incidence 1:20,000

3. Etiology/pathogenesis:
   - **PKHD1** gene, 6p, fibrocystin

   **PKHD1** = polycystic kidney and hepatic disease gene 1; provides instructions for fibrocystin
4. Pathology:
bilateral, reniform shape, enlarged, cysts in the cortex and medulla
- cross-section: sponge-like appearance
- saccular dilatation of collecting tubules

Liver:
- cysts + portal fibrosis + proliferation of portal bile ducts
- malformation of the liver: expanded portal area (fibrosis), bile ducts proliferation (tortuous dilated)

5. Tests:
radiology

6. Prognosis:
renal/liver failure at birth, infancy, juvenile

7. Treatment:
transplantation
APKD – Adult Polycystic Kidney Disease - 1

1. Typical presentation: asymptomatic or pain, colic, mass, hemorrhage, hematuria, progressive renal failure, polyuria, hypertension, low proteinuria (<2g)

2. Epidemiology: common
   - 1:400-1000 live births
   - 6-10% of ESRD (end stage kidney disease) in North America/Europe
   - 1/800-1000 population carries a mutation

3. Etiology/pathogenesis: autosomal DOMINANT

APKD – genetics

- High penetrance
- Genetically heterogeneous: Chromosomes 16 (PKD1) and 4 (PKD2), other?
- PKD1 – 85%, earlier onset of renal failure, more severe
- PKD2, later onset of renal failure
- PKD1 – polycystin 1, function? Cell-cell, cell-matrix interactions
- PKD2 – polycystin 2, regulation of intracellular Ca²⁺ levels

Abnormalities in cell differentiation

Ciliopathy (mechanosensors) – defects in mechanosensing
“Cilia=cellular GPS system”

APKD – gross pathology

- [Images of kidney pathology]
APKD – Adult Polycystic Kidney Disease - 2

4. Pathology: bilateral, reniform (kidney-like) shape
   - Enlarged mass of cysts in the cortex and medulla, functioning nephrons dispersed between the cysts, hepatic cysts (40%) intracranial berry aneurysms (4-10% of deaths)
   - Mitral valve prolapse (20-25%)

5. Tests: radiology

6. Prognosis: renal failure in middle age/later life depending on mutation

7. Treatment: transplantation

ADPKD: intracranial aneurysm
   - "berry aneurysm"
   - The most serious possible complication of PKD
   - 3 – 7%

Aneurysm = bulging blood vessel due to weakening of the blood vessel wall
Rupture with intracranial bleeding
Renal cystic diseases

- Age
- Incidence
- Complications
  - Gross appearance: reniform (kidney-shape-like) versus irregular shape
  - Bilateral versus unilateral versus segmental

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Cystic diseases

<table>
<thead>
<tr>
<th></th>
<th>PEDIATRIC DYSPLASIA</th>
<th>CHILDHOOD</th>
<th>ADULT</th>
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<tbody>
<tr>
<td>incidence</td>
<td>1:1000-2000</td>
<td>1:20,000</td>
<td>1:500-1:1000</td>
</tr>
<tr>
<td>bilateral</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>segmental</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reniform shape</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ureter abnormalities</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver abnormalities</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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Medullary diseases with cysts

1. Medullary sponge: relatively common, innocuous
2. Nephronophthisis-medullary cystic disease complex: pediatric onset CKD (chronic kidney disease) autosomal recessive
Acquired (dialysis-associated)
cystic disease

Cortical & medullary cysts
Renal Cell Carcinoma:
7%/10yrs

Simple cysts

- Very common
- Usually asymptomatic
- Multiple or single
- Differential Diagnosis
  - cystic cancer
  - Hemorrhage, pain, calcifications

Kidney tumors

Adults
- benign: oncocytoma, angiomyolipoma
- malignant: renal clear cell carcinoma,
  papillary renal cell carcinoma, chromophobe renal carcinoma
- urothelial carcinoma of the renal pelvis/ureter

Children:
- malignant: Wilms tumor
Kidney tumors

• All tumors presumed malignant until proven otherwise !!!
• Pediatric versus adults
• Renal parenchymal versus urothelial

Adults: benign kidney tumors

• Oncocytoma
• Angiomyolipoma

Oncocytoma

• Benign
• 10% of renal tumors
• Origin: distal nephron

Gross:
mahogany brown
with central scar
Abundant mitochondria by electron microscopy

Oncocytoma - microscopic
Eosinophilic (pink) cytoplasm
Abundant mitochondria by electron microscopy

Angiomyolipoma

- Vessels/smooth muscle/fat (radiologic diagnosis)
- Tuberous sclerosis, some sporadic
- Tuberous Sclerosis:
  TSC1 - Hamartin 9q34
  TSC2 - Tuberin 16p13
  benign tumors: brain, kidneys, heart, liver, eyes, lungs, skin
  larger tumors can rupture with bleeding

Angiomyolipoma - gross

Angiomyolipoma - microscopic
fat, smooth muscle, poorly formed vessels
benign, can rupture with bleeding
Renal Cell Carcinoma [RCC] -1

1. Clinical presentation - triad: painless hematuria, palpable abdominal mass, dull flank pain
   - hematuria in >50% of cases, incidentally discovered
   - malaise, weakness, weight loss
paraneoplastic syndrome: hypercalcemia, hypertension, polycythemia, Cushing syndrome [↑ cortisol]
presentation with metastases: lungs, bones, inferior vena cava involvement

Renal Cell Carcinoma [RCC]– 2

2. Epidemiology:
   - 2-3% of all cancers in adults
   - 65,000 new cases/year in the US; 40% die of the disease
   - 6-7th decade
   - M>F, 2:1
   - risk factors: tobacco, obesity, HTN, occupational cadmium exposure
   - acquired cystic disease 30-fold increase of risk
   - most are sporadic
   - familial 4%

Renal Cell Carcinoma - genetics

- Most sporadic
- familial 4%
  - younger age
  - multifocal
  - genetic testing

studies of familial cancers has provided molecular insights into the pathogenesis of renal cancers
Renal Cell Carcinoma – 3

3. Etiology/pathogenesis:
   Clear cell type:
   - 3p, somatic mutation/hypermethylation induced inactivation of the VHL gene (tumor suppressor gene)
   Loss of VHL gene results in accumulation of the transcription factor HIF-1α and over-expression of HIF-1α target genes, which facilitate cellular adaptation to tissue hypoxia.
   VHL gene in development of both sporadic and familial clear cell RCC
   Origin from proximal tubular epithelium

von Hippel-Lindau (VHL) syndrome associated with RCC clear cell type

- 1:40,000, autosomal dominant
- Age @ onset 37 years versus 61 years in sporadic RCC
- Multiple bilateral cysts & tumors in 40-60% of affected people
- Tumors with high vascularity + clear cells
- Hemangioblastoma (cerebellum, retina)
- Angiomas of the retina
- Pheochromocytomas (some), other
- Many different alterations in the VHL gene (3p25) with some correlation between specific inactivation and phenotype

Control of HIF-1α by VHL in Normoxic Conditions

- Under normoxic conditions
  VHL ubiquitinates HIF-1α, leading to ubiquitin-mediated proteolysis and degradation by the proteasome
Control of HIF-1α by VHL in Hypoxic Conditions

- In hypoxic cells, such as those found in tumors, HIF-1α ultimately initiates the transcription of hypoxia-induced genes, including those which promote
  - cell survival under anaerobic conditions
  - angiogenesis
  - metastasis

Renal Cell Carcinoma (RCC) – 4

4. Pathology dependent on carcinoma type:
RCC clear cell type, most common, 65%

- yellow-orange
  - “adrenal gland-like”

- Invasion into renal vein at advanced stages
- cells with clear cytoplasm, highly vascular, delicate, “chicken wire-like” blood vessels

Renal Cell Carcinoma (RCC) – 3&4

Papillary RCC 10-15%

3. Etiology/pathogenesis:
- trisomies 7, 16, 17
- chromosome 7 – MET oncogene
- hereditary (Familial) - multiple bilateral proximal nephron origin

4. Pathology:
- cystic
- papillary architecture
Renal Cell Carcinoma (RCC) – 3&4

3. Etiology/pathogenesis:
multiple chromosomal losses
distal nephron origin

4. Pathology:
    prominent cell membrane "vegetable-like"
morphologic overlap with oncocytoma

Chromophobe RCC, 5%

5. Laboratory tests: radiology
    • some: paraneoplastic syndrome
        hypercalcemia, hypertension, polycythemia, Cushing syndrome

6. Prognosis: stage and type dependent
    5 year survival estimates based on stage
    • Stage I 96%
    • Stage II 82%
    • Stage III 64%
    • Stage IV 23%

Clear cell RCC worse prognosis
papillary RCC better than clear cell RCC
chromophobe RCC better than clear cell and papillary

Chromophobe RCC: H&E (above)
"vegetable"-like cells
Electron microscopy (right) - vesicles

Chromophobe renal carcinoma

Clear cell carcinoma

Renal Cell Carcinoma – 5
7. Treatment: surgery mainstay, targeted therapies evolving
- RCC is extremely chemo-resistant
- surgery including metastasectomy (lungs)
- cytoreductive surgery + immunotherapy/targeted therapy
- immunotherapy: IL-2, IFN-α, checkpoint inhibitors
- targeted therapies:
  - multikinase inhibitors (Sunitinib, Sorafenib)
  - monoclonal antibodies to VEGF (Bevacizumab)
  - mTOR inhibitors (Temsirolimus, Everolimus)
**Immune checkpoints** are regulators of the immune system. These pathways are crucial for self-tolerance, which prevents the immune system from attacking cells indiscriminately.

Inhibitory checkpoint molecules are targets for cancer immunotherapy due to their potential for use in multiple types of cancers.

Currently approved checkpoint inhibitors block CTLA4 (Cytotoxic T-lymphocyte-Associated protein 4), PD-1 (Programmed Death 1) and PD-L1 (Programmed Death ligand 1).


Checkpoint therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how cancer can be managed.

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**Figure:** Upper left: Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as "non-self." A protein functioning as a T-cell accelerator is also required for T cell activation. CTLA-4 functions as a brake on T cells that inhibits the function of the accelerator.

Lower left: Antibodies (green) against CTLA-4 block the function of the brake leading to activation of T cells and attack on cancer cells.

Upper right: PD-1 is another T-cell brake that inhibits T-cell activation.

Lower right: Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells.

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**Adult renal tumors - summary**

- Malignant until proven otherwise
- Surgical treatment = mainstay, targeted and immune therapies evolving
- Prognosis:
  - stage, tumor histology
  - presence of nodal metastases
  - evidence of metastatic disease at presentation
  - patterns of metastases: lung, bone, brain, liver and adrenal gland
- Classification evolving, role of molecular studies
Urothelial carcinoma

- 5-10% of renal tumors = urothelial carcinoma
- adults
- renal pelvis, ureter, frequently also concomitant urinary bladder cancer
- hematuria
- analgesic nephropathy = risk factor, separate lecture…

Wilms tumor - 1

1. Clinical presentation:
   - mass 75%
   - 25% with other developmental abnormalities; syndromic in 10%:
     - Beckwith-Wiedemann syndrome: Wilms tumor, macroglossia, organomegaly, hemihypertrophy (extremities)
     - Denys-Drash syndrome: Wilms tumor, gonadal dysgenesis, renal (mesangial sclerosis)
     - WAGR complex: Wilms tumor, aniridia, genitourinary abnormalities, mental retardation

2. Epidemiology:
   - pediatric, most common kidney tumor
   - children <10 yo; 2-5 yo

3. Pathogenesis:
   - mutations WT1, WT2, loss of function mutation
   - recapitulates nephrogenesis (development of the kidney)
   - nephrogenic rests = putative precursor lesion of Wilms tumor

Wilms tumor - histology

Wilms' tumor triphasic histology: undifferentiated blastema*, tubules*, fibroblast-like stroma'

Wilms tumor - an example of how cancer arises through development gone awry
4. Pathology: recapitulates nephrogenesis
   - undifferentiated blastema (undifferentiated small round blue cells),
   - attempts to differentiate: epithelial - abortive glomeruli/tubules
   - stromal cells spindle cell (fibroblast-like or myxoid)

5. Laboratory tests:
   - radiologic studies

6. Prognosis: excellent, 90% five years survival

7. Treatment:
   - surgery with/without chemotherapy depending on stage
   - chemosensitive

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Pediatric malignancy 0 to 4 years

• Leukemia – blood
• Retinoblastoma – eye, neuronal origin
• Neuroblastoma – adrenal gland
• Wilms’ tumor – kidney

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A 2 yo boy is brought to pediatrician because his mother palpated
   “a bulging mass” while bathing him. What best applies to the case?

a. This tumor most likely is composed of clear cells
b. This tumor typically shows loss of short arm of chromosome 3
c. This tumors is most likely highly chemoresistant
d. This tumor is chemosensitive
e. Cysts, disorganized renal parenchyma with immature tubules and cartilage
An infant is diagnosed with an enlarged left kidney – shown. Most likely:

a. This lesion will respond to chemotherapy
b. This is autosomal dominant lesion
c. This is a congenital disorder with recessive inheritance
d. Cystic lesion, disorganized renal parenchyma with immature tubules and cartilage
e. Kidney sections show undifferentiated blastema, tubules and stroma

Immature, persistent abnormal structures, aberrant nephronic differentiation, biologically benign cysts enlarge but there is NO invasion of nearby tissues, no metastatic potential

Undifferentiated blastema, “embryonal”, “small blue cells”, attempts to recapitulate nephrogenesis, biologically malignant, uncontrolled growth, can invade nearby tissues and metastasize

Development gone awry:
Wilms tumor (malignancy) versus cystic dysplasia (benign, developmental)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Wilms tumor</th>
<th>Cystic dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformation</td>
<td>Increased risk</td>
<td>100%</td>
</tr>
<tr>
<td>Histogenesis</td>
<td>Attempts to recapitulate nephrogenesis</td>
<td>Aberrant nephronic differentiation</td>
</tr>
<tr>
<td>Histology</td>
<td>Undifferentiated blastema, “embryonal”, “small blue cells”; immature, persistent abnormal structures</td>
<td></td>
</tr>
<tr>
<td>Behavior</td>
<td>Malignant</td>
<td>Benign</td>
</tr>
<tr>
<td>Invasion of nearby tissues</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Metastasis potential</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cysts</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetics</td>
<td>Mutations: somatic, germ line</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Bilateral</td>
<td>5-10% synchronous (simultaneously); metachronous (one after the other)</td>
<td>Bilateral associated with Potter’s syndrome</td>
</tr>
</tbody>
</table>
Development:
- The process by which a single cell (the fertilized egg) becomes a fully formed and functional infant.
- Its course is very complex and involves cellular proliferation and differentiation, tissue twisting and folding, cell cluster expansion and regression.

Development gone awry:
- Developmental abnormalities/defects: cystic dysplasia
- Cancer: Wilms tumor

Cancer:
- Uncontrolled cell growth (proliferation), failure to differentiate into a particular cell type,
- Resistance to cell death, increased cellular motility, and formation of new blood vessels
- All of these processes are utilized during development, and all are misused in cancer. Hence, there are similarities between cancer and normal development, particularly in pediatric cancers.

Childhood tumors:

1. Relationship between congenital malformation and increased risk of tumors
   - Beckwith-Wiedemann syndrome, WAGR complex, Denys-Drash syndrome
   - Teratogenesis (abnormal development) and oncogenesis (tumor induction)

2. Prevalence of genetic abnormalities or familial syndromes that predispose to cancer
   - Tendency of fetal and neonatal malignancies to regress spontaneously or to undergo "differentiation" into mature elements

3. Better survival or cure of many childhood tumors

   Histologic similarity between tumor and developing organ
   - Wilms tumor recapitulates nephrogenesis

During a radiologic workup for gall bladder stones, a 65 yo male was found to have a 5 cm mass in his right kidney.

a. This is most likely oncocytoma
b. This is most likely a benign tumor
c. Chemotherapy will be effective
d. Surgery consultation will be scheduled
e. Tumor’s morphology shows abortive glomeruli/tubules and stroma
Questions?
mpicken@lumc.edu