MECHANISMS OF HUMAN DISEASE: LABORATORY SESSION
RENAL PATHOLOGY
April 12, 2013

Faculty Copy

GOAL:

1. **Describe the basic morphologic and pathophysiologic changes in various diseases of the kidney.**

2. **Describe and correlate symptoms and signs of a disease with the structural changes in diseased organs.**

OBJECTIVES:

1. **Describe the morphologic characteristics of infectious diseases of the kidney.**

2. **Describe the morphologic characteristics of malignant tumors of kidney.**

3. **Describe the morphologic characteristics of amyloidosis of the kidney.**

4. **Describe the morphologic characteristics of diabetic nephropathy.**

5. **Describe the morphologic characteristics of IgA nephropathy.**

CASE 1

CHIEF COMPLAINT:
"My back hurts."

HISTORY:
A 32-year-old woman presents to the emergency room with acute onset of fever, chills, and right flank pain. She has also had nausea and vomiting and has been unable to keep any food down for the last day. On further questioning she notes that she developed dysuria and urinary freqency several days prior.

PHYSICAL EXAMINATION:
Temp 102.1^0 F, BP 92/56, P 112
Lungs and heart exams are normal, aside from tachycardia. On abdominal exam she has suprapubic tenderness to palpation. There is marked tenderness at the right costovertebral angle.

1. Develop a problem list

Fever
Costovertebral angle tenderness/flank pain
Nausea/vomiting
Tachycardia
Low blood pressure (though we do not know her baseline)
Dysuria
Suprapubic tenderness

2. Develop a differential diagnosis for the constellation of problems.

Acute pyelonephritis
Cystitis
Gastroenteritis

3. What diagnostic work-up is recommended?

Urinalysis
Urine culture

UA w/Micro

Color	Amber [YELLOW]	
pH	6.0	[4.5-8.0]
Spec Gravity	1.030	[1.003-1.035]
Protein	Neg	[NEG]
Blood	Trace	[NEG]
Glucose	Neg	[NEG]
Ketones	NEG	[NEG]
Bilirubin	NEG	[NEG]
Urobilinogen	0.2	[0.2-1.0] eu/dl
Nitrate	POS	[NEG]
Leukocyte esterase	POS	[NEG]
RBC	2-5	[0-2] /hpf
WBC	>150	[0-5] /hpf
WBC casts	Few	

4. Identify the organ. Describe the characteristic pathologic changes in the virtual microscopy slide.

Section of the kidney shows an infiltrate of inflammatory cells (predominantly neutrophils) within the interstitium and tubules.

5. What is your diagnosis?

Acute pyelonephritis

Urine culture results:
> 100,000 colonies *E. coli*

6. What conditions predispose to this process?

Urinary obstruction, intrumentation, vesicoureteral reflux, pregnancy, patient age and sex (ages 1-40 more common in females; after age 40 incidence increases in males secondary to prostatic hypertrophy and instrumentation), pre-existing renal lesions, diabetes mellitus, immunosuppression/deficiency.

7. What are complications of this process?

Bacteremia, sepsis, papillary necrosis, pyonephrosis (obstruction), perinephric abscess

8. In what other conditions can WBC casts be seen?

Essentially in any interstitial inflammatory process, such as acute interstitial nephritis. Acute interstitial nephritis usually represents an adverse reaction to a drug. It is often an immune mediated hypersenstivity reaction where the drug acts as a hapten. During secretion by tubules, the hapten binds to cytoplasmic or extracellular component of the tubular cells and becomes immunogenic. Resultant tubulointerstitial injury is caused by IgE and cell-mediated immune reaction to tubular cells. Pathologic abnormalities are usually in the interstitium and include edema and mononuclear cell, eosphinophil, and sometimes neutrophilic infiltrates.
The clinical manifestation of acute interstitial nephritis include fever, peripheral eosinophilia, rash. Acute renal failure may develop. May see urinary eosinophils (and casts on urinalyses. Recognition and withdrawal of the offending drug is key to recovery.

CASE 2

<u>CHIEF COMPLAINT</u>:

"I'm having pain."

HISTORY:
A 63-year-old man presents with right flank pain that has been ongoing for the past several months. He has felt more tired than usual, but otherwise feels "ok".

PHYSICAL EXAMINATION:
The abdomen is soft and non-tender. He has right costovertebral tenderness on palpation. There is no vertebral tenderness.
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1. Develop a differential diagnosis of "costovertebral pain"

   Acute pyelonephritis
   Chronic pyelonephritis
   Nephrolithiasis
   Renal cancer
   Musculoskeletal pain/injury

2. What is your recommended initial diagnostic evaluation?

   Urinalysis

UA w/Micro		
Color	Yellow	[YELLOW]
pH	6.0	[4.5-8.0]
Spec Gravity	1.020	[1.003-1.035]
Protein	Neg	[NEG]
Blood	**Mod**	**[NEG]**
Glucose	Neg	[NEG]
Ketones	Neg	[NEG]
Bilirubin	Neg	[NEG]
Urobilinogen	0.2	[0.2-1.0] eu/dl
NITRATE	Neg	[NEG]
LEUKOCYTES	Neg	[NEG]
RBC	**25-50**	**[0-2] /hpf**
WBC	2-5	[0-5] /hpf

3. What are the most common causes of hematuria in men >60 years old?

   Benign prostatic hyperplasia
   Bladder tumor
   Kidney tumor
   Acute urinary tract infection

4. Describe the characteristic gross organ morphology

Yellow-gray spherical mass distorts the renal anatomy. Foci of hemorrhage, necrosis may be present.

5. Identify the organ. Describe the characteristic pathologic changes in the virtual microscopy slide.

Section of kidney contains an infiltrating clear cell carcinoma. The tumor cells are rounded or polygonal shaped with abundant clear or granular cytoplasm (on special stains the cytoplasm stains for fat and glycogen).

6. What is your diagnosis?

Renal Cell Carcinoma, clear cell type

most common type of renal cancer

"classic triad" of pain, palpable mass, and hematuria (often microscopic and intermittent) present in only 10% of cases

7. Which genetic mutations/syndromes are associated with this lesion? What are the clinical implications?

In 98% of cases of clear cell (non-papillary) carcinoma, whether familial or sporadic, there is loss of sequences on short arm of chromosome 3

- **a deletion (3p-) or unbalanced chromosomal translocation (3;6, 3;3, 3;11) results in the loss chromosome 3 overlapping the region harboring the VHL gene. VHL, a tumor suppressor gene, is inactivated (In some cases it is mutated).**

Problem – VHL protein is a critical component of a cellular pathway that couples changes in oxygen availability to gene expression through regulation of a transcription factor - hypoxia inducible factor (HIF)

- **Under normal cellular oxygen conditions, VHL protein binds to HIF which is tagged for degradation**
- **In hypoxic conditions, HIF is not degraded and accumulates stimulating the production of growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)**

Cells deficient in VHL inappropriately upregulate HIF. As a result - transcription and production of pro-angiogenic proteins VEGF and TGF are upregulated leading to stimulation of cell growth and angiogenesis. The neoplasm is provided growth and angiogenic factors that contribute to its survival

Clinical implications: Clear cell renal cancer is among the most resistant of tumors to therapy. Until 2005 only a single treatment, high dose interleukin-2, had been approved by FDA for treatment of metastatic disease. IL-2 is toxic, its benefits remain unclear.
Understanding the molecular pathway and biology of renal cell cancer has led to development of new drug therapies

- **Sunitinib and sorafenib block VEGF pathway and have been approved by the FDA for use in advanced renal cell carcinoma . They have been shown to improve progression-free survival in patients. Additional drugs are being developed.**

Reference: Brugarolas, NEJM 356 (2): 185, January 11, 2007

CASE 3

CHIEF COMPLAINT:
"My feet and legs are swelling."

HISTORY:
A 41-year-old woman presents with complaints of foot and leg swelling gradually worsening over the past month. She also notices that she is "puffy around the eyes" after waking up in the morning.

PHYSICAL EXAMINATION:
BP 140/88, Pulse 80. There is bilateral lower extremity edema extending to the thighs and bilateral hand edema. Remainder of the physical exam is unremarkable.

LABS:

BUN	18 mg/dl
Creatinine	1.7 mg/dl
Albumin	1.9 mg/dl

UA w/Micro

Color	Yellow	[YELLOW]
pH	6.0	[4.5-8.0]
Spec Gravity	1.020	[1.003-1.035]
Protein	**4+**	**[NEG]**
Blood	Neg	[NEG]
Glucose	Neg	[NEG]
Ketones	Neg	[NEG]
Bilirubin	Neg	[NEG]
Urobilinogen	0.2	[0.2-1.0] eu/dl
Nitrate	Neg	[NEG]
Leukocyte	Neg	[NEG]
RBC	0	[0-2] /hpf
WBC	0	[0-5] /hpf

+oval fat bodies

24-hour estimated urine protein excretion: 6 grams

1. What is your preliminary diagnosis?

Nephrotic Syndrome

- **Massive proteinuria (>3.5 gram or more protein daily)**
- **Hypoalbuminemia (plasma albumin <3gm/dL)**
- **Generalized edema**
- **Hyperlipidemia and hyperlipiduria**
  - **What is an "oval fat body"?**
    - **Renal tubule epithelial cells in which globules of lipid have become visible**
    - **Frequently, but not exclusively, associated with nephrotic syndrome**

2. What is included in the differential diagnosis of this syndrome in adults?

Primary Glomerular Disease:

- **Membranous glomerulonephritis**
- **Lipoid nephrosis (minimal change disease)**
- **Focal segmental glomerulosclerosis**
- **Membranoproliferative glomerulonephritis**

Systemic Diseases:

- **Diabetes**
- **Amyloid**
- **SLE**
- **Drugs**
- **Infections**
- **Malignancy**

A thorough history and physical may suggest the etiology of nephrotic syndrome and select serologic studies may help determine or support diagnosis. Definitive diagnosis is by renal biopsy

3. Identify the organ. Describe the characteristic pathologic changes in the virtual microscopy slide.

Section of kidney demonstrates modest deposition of homogeneous eosinophilic material (amyloid) noted primarily in the walls of blood vessels
Some glomeruli contain focal amphorous amyloid deposits in the mesangium.

4. What additional stain(s) may help you make the diagnosis?

Congo red stain with examination under polarized light.

5. What is your diagnosis?

Amyloidosis involving the kidney.

Extensive deposition of amyloid fibrils in mesangia and glomerular basement membrane renders glomerular filter leaky to plasma proteins and the development of proteinuria. Progressive obliteration of glomeruli ultimately leads to renal failure and uremia. In most reported cases of patients with amyloid, renal amyloidosis is the major cause of death
Most commonly renal amyloid is of light-chain (AL) or AA type

CASE 4

CHIEF COMPLAINT:
"I'm here for my check-up."

HISTORY:
The patient is a 69-year-old man with a history of hypertension, diabetes mellitus, type 2, and coronary artery disease. He has known proteinuria and chronic kidney disease. He has no specific complaints.

PHYSICAL EXAMINATION:
BP 150/72; Pulse 60. Heart, lung, and abdominal exams are unremarkable. He has decreased sensation and proprioception of his feet.

Lab Data

BUN	36 mg/dl
Creatinine	2.7 mg/dl
Hemoglobin A1C	9%
Urinalysis	3+ protein

1. Identify the organ. Describe the characteristic pathologic changes.

   Section of kidney shows multiple glomeruli with thickening of the glomerular basement membrane; increase in the mesangial matrix; nodular glomerulosclerosis (nodular lesions within the mesangium); and glomeruli with diffuse sclerosis.
   Arteriolar sclerosis is noted.
   In some sections there is tubular atrophy and interstitial fibrosis.

2. What is your diagnosis?

(Kimmelstiel-Wilson nodules) Diabetic kidney - nodular glomerulosclerosis.

Leading cause of end stage renal disease in the US

- **ACE inhibitors both lower protein excretion and slow the rate of disease progression in patients with microalbuminuria and in those with overt nephropathy**
- **Blood pressure, glycemic, and lipid control all important in slowing disease progression**

CASE 5
(no virtual microscopy slide)

History of Present illness
A 17-year-old male presents to his physician with the chief concern of red urine. Six months ago he developed a "cold" and 1 day later he noticed that his urine was red. The urine cleared after several days . He did not tell his parents. He noticed reddish urine for several days about 3 months ago but then the urine returned to a normal color. He again developed red urine 1 day ago. Now concerned, he told his parents who brought him in for evaluation.
He has not had any recent trauma and has not strenuously exercised during the past week. He has had no change in his urine output. He has had no gum bleeding, nose bleeds, hematochezia or melena. He has no abdominal or flank pain.
He feels well. He takes no medications.
His mother, father, and 3 siblings are all healthy.

Physical exam:
Normally developed male BP 108/62, pulse 72, afebrile
Heart and lung exams are normal. Abdominal exam is normal; there is no suprapubic tenderness.
There is no flank mass or tenderness. Genital exam is normal. There are no skin rashes.

Laboratory Data

Urinalysis

Color	Red	[YELLOW]
pH	6.0	[4.5-8.0]
Spec Gravity	1.020	[1.003-1.035]
Protein	1+	[NEG]
Blood	**Large**	**[NEG]**

Glucose	Neg	[NEG]
Ketones	Neg	[NEG]
Bilirubin	Neg	[NEG]
Urobilinogen	0.2	[0.2-1.0] eu/dl
Nitrate	Neg	[NEG]
Leukocytes	Neg	[NEG]
RBC	**>100**	**[0-2] /hpf**
WBC	2-5	[0-5] /hpf

BUN	12 mg/dl
Creatinine	0.5mg/dl

CBC, PT, PTT normal

1. List the most common causes of hematuria in 0-20 year olds.

Glomerular disease/glomerulonephritis
- **Glomerular causes of asymptomatic recurrent hematuria**
  - **IgA nephropathy**
  - **Alport Syndrome**
  - **Benign familial hematuria**

Acute urinary tract infection
Congential urinary tract anomolies

Examination of repeat urinalysis shows the presence of RBC casts

2. What is the significance of this finding?

Indicates glomerular cause of hematuria

3. Describe the microscopic findings.

On PAS stain there is mesangial proliferation - "mesangial proliferative glomerulonephritis". Mesangial deposition of IgA is present on immunofluorescence. Electron microscopy reveals discrete electron dense deposits in mesangium.

4. What is the diagnosis?

IgA Nephropathy (Berger Disease)

Most common type of glomerulonephritis world-wide.
Affects children and young adults most commonly.
Patients generally present with episodic gross (and microscopic) hematuria, which often develops/ occurs within 24 hours of mucosal (usually upper respiratory tract) infection. It is an isolated renal disease. RBC casts may be seen on urinalysis.
Most patients have an indolent course, though some develop develop acute renal failure (crescentic glomerulonephritis) and a subset develop progressive renal disease and end stage renal disease.
In children it may be systemic: Henoch Schoenlein Purpura

5. What is Henoch-Schonlein Purpura?

A systemic vasculitis with IgA deposition in tissues, including mesangial cells
It is more common in children <5 years old and usually follows upper respiratory tract infection
A characteristic clinical tetrad consists of purpuric rash (over extremities), athralgias (knees and ankles), abdominal pain/GI bleeding, and renal disease (gross or microscopic hematura, proteinuria, nephrotic syndrome)
It has an overall good prognosis in children, though adults may have more severe renal manifestations.